All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

AWMSG ADVICE PARTIALLY SUPERSEDED BY NICE GUIDANCE (TA323)

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(Refer to NICE website for full guidance on NICE recommendations, including any specific restrictions on the use of the technology)

Final Appraisal Report

Epoetin theta (Eporatio®▼)

Ratiopharm was acquired by Teva Pharmaceutical Industries Limited in August 2010

Advice No: 1610 – October 2010

Recommendation of AWMSG

Epoetin theta (Eporatio®▼) is recommended as an option for restricted use within NHS Wales for the treatment of adult patients with symptomatic anaemia associated with chronic renal failure only.

AWMSG is of the opinion that epoetin theta (Eporatio®▼) is not suitable for shared care within NHS Wales for the above indication.

Epoetin theta (Eporatio®▼) should be prescribed by brand name to avoid automatic substitution and therefore help with pharmacovigilance.

Epoetin theta (Eporatio®▼) is not recommended for use within NHS Wales for the treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy. The case for clinical effectiveness of epoetin theta (Eporatio®▼) has not been proven in this indication.

Statement of use:
No part of this advice may be used without the whole of the advice being quoted in full.

This report should be cited as:
All Wales Medicines Strategy Group Final Appraisal Report
epoetin theta (Eporatio®▼) October 2010

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday 13th October 2010

The recommendation of AWMSG is:

Epoetin theta (Eporatio®▼) is recommended as an option for restricted use within NHS Wales for the treatment of adult patients with symptomatic anaemia associated with chronic renal failure only.

AWMSG is of the opinion that epoetin theta (Eporatio®▼) is not suitable for shared care within NHS Wales for the above indication.

Epoetin theta (Eporatio®▼) should be prescribed by brand name to avoid automatic substitution and therefore help with pharmacovigilance.

Epoetin theta (Eporatio®▼) is not recommended for use within NHS Wales for the treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy. The case for clinical effectiveness of epoetin theta (Eporatio®▼) has not been proven in this indication.

Additional note:

For the purposes of this appraisal, non-myeloid malignancies are taken to mean non-haematological tumours as confirmed with the company.

People who are currently being treated with epoetin theta (Eporatio®▼) for symptomatic anaemia in adult cancer patients should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.

2.0 PRODUCT DETAILS

Licensed indication	Treatment of symptomatic anaemia associated with chronic renal failure in adult patients[1]. Treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy[1].
Dosing	Epoetin theta can be administered subcutaneously (SC) or intravenously (IV). Refer to the summary of product characteristics (SPC) for further information on method of administration and dosing guidance according to indication[1].
Market authorisation date	29 October 2009[2].
UK Launch date	1 December 2009[2].

3.0 DECISION CONTEXT

3.1 Background

Anaemia is common in individuals with chronic renal failure (CRF) due to insufficient production of erythropoietin, a hormone secreted from the kidney to increase the blood concentration of haemoglobin (Hb)-containing red blood cells[3]. In cancer patients, anaemia can occur as a result of the disease itself or as a complication of chemotherapy. Platinum-based treatments, for example, can damage renal tubular cells, which are responsible for endogenous erythropoietin production[3]. Estimated prevalence and incidence of renal and chemotherapy-related anaemia is outlined in section 7.0.

Treatment of anaemia with human erythropoietin produced by recombinant DNA technology (epoetin) ameliorates symptoms and reduces the need for blood transfusions[4]. Epoetin theta is one of several epoetin treatments available for use as erythropoiesis-stimulating agents (ESAs). Variations in their glycosylation patterns distinguish synthetic epoetins from each other and from human serum erthyropoetin[5, 6]. The European Medicines Agency (EMA) treats epoetin theta as distinguishable from other ESAs; it is not classified as a similar biological medicinal product (biosimilar)[3].

3.2 Comparators

Short acting:

- epoetin beta (NeoRecormon®)
- epoetin alfa (Eprex®; Binocrit®▼)
- epoetin zeta (Retacrit®▼). Not recommended for used in NHS Wales: see section 2.3.

Longer acting:

- darbepoetin alfa (Aranesp®)
- methoxy polyethylene glycol-epoetin beta (Mircera®▼).

3.3 Guidance and related advice

- NICE technology appraisal guidance 142: Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia (May 2008)[7]. This guidance does not recommend the routine use of epoetin alfa, epoetin beta or darbepoetin alfa. Use of these ESAs to treat anaemia is recommended only in ovarian cancer patients undergoing platinum-based chemotherapy, or in patients receiving cancer treatment who cannot be given blood transfusions and where anaemia is likely to impact on survival. No other epoetins are covered by this guidance, nor is the use of epoetins in anaemia caused by CRF.
- NICE clinical guideline 39: Anaemia management in people with chronic kidney disease (September 2006)[8]. This guideline recommends that the management of anaemia in chronic kidney disease should be considered in adults with Hb levels ≤ 11 g/dl. Treatment with ESAs should be offered to patients who are likely to benefit in terms of quality of life and physical function. The guideline states that there is no evidence to distinguish between ESAs in terms of efficacy.
- AWMSG Final Appraisal Report: methoxy polyethylene glycol-epoetin beta (Mircera®▼, October 2009). Methoxy polyethylene glycol-epoetin beta is recommended as an option for use within NHS Wales for the treatment of adults with symptomatic anaemia associated with chronic kidney disease[9].
- AWMSG Final appraisal report: Epoetin zeta (Retacrit®▼, June 2010). Epoetin zeta (Retacrit®▼) is not recommended for use within NHS Wales for the treatment of anaemia associated with chronic kidney disease or reduction of transfusion requirements in adult patients receiving chemotherapy[10]. The case for cost effectiveness was considered not to have been proven[10].

4.0 SUMMARY OF EVIDENCE ON CLINICAL EFFICACY

The company submission detailed nine clinical trials as evidence of clinical efficacy[11]: six in patients with chronic renal failure[12-17] and three in cancer patients undergoing chemotherapy[18-20].

4.1 Studies in patients with chronic kidney disease

4.1.1 Correction phase studies

Details of two randomised, active-controlled, double-blind phase II trials were submitted[11]. Studies XM01-04 and XM01-05 were carried out in adult CRF patients with anaemia, who were either not receiving dialysis (n=134) or on haemodialysis (n=150) respectively. In both studies patients received a fixed dose of epoetin theta or epoetin beta; several treatment groups received epoetin theta at different fixed doses (20–120 IU/kg SC as part of XM01-04; 40–120 IU/kg IV as part of XM01-05) whilst a single group received a fixed dose of epoetin beta equivalent to the lowest dose of epoetin theta.

In both studies the primary outcome was the dose-dependent average weekly increase in Hb within the fixed dosed period. The primary objective was a statistically significant difference between Hb levels of patients treated with the lowest epoetin theta dose (20 IU/kg and 40 IU/kg in XM01-04 and XM01-05 respectively) and the highest epoetin theta dose. In both studies this objective was met[11]. Relevant secondary outcomes demonstrated that equivalent doses of epoetin theta and epoetin beta resulted in similar times to Hb response and a similar percentage of responding patients.

4.1.2 Maintenance phase studies

Details of two randomised, active-controlled, double-blind phase III trials were submitted[11].

XM01-06 was a study in adult CRF patients being treated for anaemia with SC epoetin beta but not yet receiving dialysis (n = 288)[11]. Following a baseline period (2 weeks), patients were randomised 1:2 to continue treatment with epoetin beta or switch to an equivalent dose of epoetin theta. This period lasted 24 weeks, during which time the dose was adjusted to maintain Hb levels within the target range (9.5–12.0 g/dl).

XM01-07 was a study in adult CRF patients (n = 270) being treated for anaemia with IV epoetin beta and receiving haemodialysis for at least six months[11]. Study periods followed the same pattern as XM01-06.

In both studies the primary outcome was the change in Hb level from baseline to the end of the treatment period; the primary objective was to demonstrate non-inferiority of epoetin theta compared with epoetin beta, defined as no statistically or clinically significant difference in the change of Hb level between the epoetin beta and epoetin theta treatment groups. This objective was met for both studies: the difference between groups was not statistically significant and was within the predetermined maximum clinically acceptable threshold of 1.0 g/dl[11]. Although the Committee of Medicinal Products for Human Use (CHMP) considered the predetermined maximum clinically acceptable difference between treatment groups of 1.0 g/dl as very tolerant, in both studies the estimated difference in Hb levels between the two treatment groups (± 0.01 g/dl) was well within this margin and was therefore considered acceptable by the CHMP[3].

4.1.3 Long-term studies

Evidence from two follow-up open-label studies was submitted[11].

XM01-08 was an extension study in renal anaemia patients (n = 223) successfully treated with SC ESA therapy during XM01-04 and XM01-06[11]. Following a 12-week pre-randomisation period, the primary objective of this study was to demonstrate equivalence of once weekly (ow) and thrice weekly (tiw)-administered epoetin theta in terms of the time-adjusted area under the curve for Hb (AUC-Hb) and mean weekly epoetin theta dose for 24 weeks. In terms of the AUC-Hb, this objective was met: there was no statistically significant difference between the two groups. In terms of mean weekly epoetin theta dose, the primary objective was not met: the two-sided 95% confidence interval for the ratio of mean weekly dose in the ow and tiw groups did not lie entirely within the predetermined equivalence range of 0.8–1.25[11]. Although no explanation is given in the company submission to AWMSG, analysis of the data by the CHMP highlighted that patients in the ow group had a lower mean dose than those in the tiw group at the beginning of the study[3].

Study XM01-09 was an extension study in renal anaemia patients (n = 124) successfully treated with intravenous ESA therapy as part of XM01-05[11]. XM01-09 primarily concerned safety and is discussed in section 4.0.

4.2 Studies in cancer patients with anaemia resulting from chemotherapy

Three randomised, double-blind, phase III trials were included in the company submission[11].

XM01-22 was a placebo-controlled study in patients (n = 186) with solid tumours or non-myeloid haematological malignancies receiving non-platinum-containing chemotherapy and with baseline Hb levels ≤ 11 g/dl[11].

Study XM01-23 was carried out in patients with low grade non-Hodgkin's lymphoma, chronic lymphocytic leukaemia or multiple myeloma who were undergoing chemotherapy and had endogenous erythropoietin deficiency. Since epoetin theta is not licensed for this indication, this study has not been considered under this section.

XM01-21 was an active- and placebo-controlled study in patients (n = 223) with solid tumours undergoing platinum-containing chemotherapy and with baseline Hb levels ≤ 11 g/dl. Patients were randomised to receive epoetin beta tiw, placebo tiw or epoetin theta ow (plus two weekly placebo injections) for 12 weeks[11]. All treatments were administered subcutaneously. The starting dose for epoetin theta was 20,000 IU/week, increased to 40,000 IU/week in patients who did not partially respond after 4 weeks of treatment and again to 60,000 IU/week if the Hb level did not reach the designated increase of ≥ 2 g/dl after the second 4-week period of treatment. The epoetin beta starting dose was 450 IU/kg per week, administered in three equal aliquots. The dose was to be doubled to 900 IU/kg per week in patients who did not partially respond after four weeks of treatment.

In studies XM01-21 and -22 the primary outcome was the number of patients with a complete Hb response, defined as an increase in Hb level of at least 2 g/dl from baseline without a blood transfusion. The primary objective was to show superiority of epoetin theta over placebo with respect to the primary outcome; in both studies this objective was met. Relevant secondary endpoints of XM01-21 concerned the differences between epoetin beta and epoetin theta in terms of change of Hb levels, number of patients with a complete or partial Hb response, and quality of life. In all cases there was no statistically significant difference between epoetin beta and epoetin theta[11].

5.0 SUMMARY OF EVIDENCE ON COMPARATIVE SAFETY

Study XM01-09 was an open, phase III study in renal anaemia patients successfully treated with intravenous ESA therapy as part of the correction phase study XM01-05 (see section 3.1)[11]. Patients received the same dose as they had been receiving at the end of XM01-05; those who had previously been treated with epoetin beta were started on the equivalent dose of epoetin theta. Treatment was administered intravenously, initially tiw but becoming twice weekly in patients with stable Hb levels. The treatment period was 36 weeks.

Primary endpoints were frequency of adverse events (AEs), frequency of study discontinuation due to AEs, and immunogenicity of epoetin theta. Reported AEs were all known effects of the underlying disease or epoetin treatment. Based on results of a pooled analysis (see below), the possibility of specific neutralising anti-epoetin theta/anti-erythropoietin reactivity development was dismissed.

A pooled safety analysis of all studies described in section 3.0 was also carried out. Consistent with XM01-09, this revealed no AEs not already associated with the underlying disease or epoetin treatment. Furthermore, there were no clinically significant differences between treatment-emergent AEs between patients treated with epoetin theta and epoetin beta[3, 11].

Studies of ESAs used to treat anaemia in cancer patients have reported a statistically significant increase in mortality in patients treated with epoetins compared with controls[21, 22].

Additionally, erythropoietin receptors are present on cells from some metastatic tumours, leading to the suggestion that erythropoietin (whether endogenous or exogenous) could enhance tumour progression[23, 24]. In light of this evidence, in June 2008 the EMA recommended safety updates to the SPC for all epoetins[25]. The view of the CHMP is that the benefits of epoetins continue to outweigh the safety risks in the approved indications, but that the decision to administer epoetins should be based on an informed assessment of the benefits against the risks on an individual basis, taking into account the type and stage of tumour, the degree of anaemia, and the patient's life-expectancy[25].

6.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- The evidence submitted for the use of epoetin theta in the treatment of chemotherapy-induced anaemia is limited, particularly in terms of comparison with epoetin beta. Study XM01-23 was carried out in patients with a diagnosis outside of the licensed indication. XM01-22 compared epoetin theta only to placebo, also not all patients in this study were relevant to the licensed indication; 37.6% of those patients had a diagnosis of NHL or MM. XM01-21 compared epoetin theta and epoetin beta but only as secondary outcomes.
- The clinical and economic evidence considers only epoetin beta as a comparator. Epoetin beta accounts for only 22% of ESA treatment in Wales[26]; other relevant comparators may offer advantages in terms of list price, dosing frequency or convenience of administration (see section 6.1.3).
- The clinical evidence includes a low proportion of peritoneal dialysis patients when compared with the Welsh population. In studies XM01-05, XM01-07 and XM01-09, 3% of patients were receiving peritoneal dialysis[11]. In Wales, peritoneal dialysis patients account for 20% of total CRF patients receiving dialysis[26].
- In the maintenance phase studies submitted, Hb levels of patients with anaemia are maintained within a target range of 9.5–12.0 g/dl[11]. This is in contrast to the Medicines and Healthcare Products Regulatory Agency (MHRA) recommended target of 10–12 g/dl[25] and the NICE recommended target of 10.5–12.5 g/dl for adults and children older than two years of age[8].

7.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

7.1 Cost-effectiveness evidence

7.1.1 Context

The company submission[11] describes base-case cost effectiveness analyses (CEAs) of epoetin theta compared against epoetin beta for five individual scenarios (Table 1). Efficacy inputs to the models relate to the proportion of patients achieving haemoglobin target concentrations, withdrawal/death rates, treatment duration, and blood transfusion rates. The key active-controlled regulatory trials provide the parameter estimates for the five populations/scenarios that have been modelled[12-15, 18]. The trial providing data for the treatment of chemotherapy recipients relates only to the treatment of patients with solid tumours receiving platinum-based chemotherapy[18]. Costs included in the analysis relate to drug acquisition (based on list prices) and blood transfusion costs. The frequency and costs of administration are assumed to be equivalent. Cost minimisation (CMA) and threshold analyses have been provided as sensitivity/scenario analyses. Further details are provided in Appendix 1.

The analysis excludes other relevant comparators as discussed in section 6.1.3. An economic analysis has not been provided specifically for the use of epoetin theta in peritoneal dialysis patients.

7.1.2 Results

The results of the base-case cost effectiveness analyses as presented in the company submission are displayed in Table 1. Epoetin theta is estimated to be cost saving in all modelled scenarios compared against epoetin beta[11].

Table 1. Company-reported cost effectiveness and cost minimisation analyses[11]

	Base-case cost effectiveness analyses			Secondary CMA
	Cost per patient at/maintained within target Hb*			Assumed equivalence
Modelled scenarios	**Epoetin theta**	**Epoetin beta**	**Difference**	**Difference**
1) Initiation of SC treatment in pre-dialysis renal patients tiw over 16 weeks	£522.87	£576.02	-£53.15	-£106
2) Initiation of IV treatment in haemodialysis patients tiw over 16 weeks	£1,255.22	£1,466.36	-£211.14	-£271
3) Maintenance SC treatment in pre-dialysis patients – ow over one year	£1,219.78	£1,253.94	-£60.78	-£161
4) Maintenance IV treatment in haemodialysis patients – ow over one year	£3,804.51	£4,330.92	-£526.41	-£497
5) Initiation of SC treatment in chemotherapy recipients – ow over 12 weeks	£3,098.71	£5,363.05	-£2,264.34	-£463
*Model 1 and 2 target: Hb = 11–12 g/dl for two successive weeks with no transfusion in previous three months. Model 3 and 4 target: Hb = 9.5–12 g/dl and no more than 1 g/dl above or below baseline level for each patient; Model 5 target: increase in Hb of > 2 g/dl with no transfusion in previous four weeks				

Under the assumption of equivalence in all domains of health outcome and drug doses (i.e. the secondary cost minimisation analysis), treatment with epoetin theta is the least costly in all modelled scenarios (Table 1). Threshold analyses indicate that, assuming equivalence in efficacy parameters, the dose (and hence cost) of epoetin beta would need to be reduced by between 15% (Model 2) and 43% (Model 5) to achieve the same mean cost per patient as for treatment with epoetin theta[11].

7.1.3 WMP Critique

Strengths of the economic evidence include:

- The analyses appropriately use current list prices for costing the ESA products.
- Secondary analyses are provided to explore a scenario of equivalence between the products for the purposes of cost minimisation and threshold analyses.

Limitations of the economic evidence include:

- The analysis is restricted to a comparison of epoetin theta against epoetin beta and fails to consider all relevant appropriate comparators that have common licensed indications and are recommended as treatment options within NHS Wales (see section 2.2 and 2.3). It should be noted that these other comparators include the Eprex® and Binocrit®▼ brands of epoetin alfa, which have lower list price-based acquisition costs per 1000 IU than epoetin theta[27], and darbepoetin alfa and methoxy polyethylene glycol-epoetin beta, which may be administered less frequently in renal patients and so may be associated with lower administration costs and greater patient convenience than other ESAs.

- The company has employed a CEA approach on the assumption that there are potentially meaningful differences between the doses received and the attainment / maintenance of target Hb levels, which would make cost minimisation analyses (CMA) potentially inappropriate. However, the reason provided for not conducting cost utility analyses is that any differences in quality adjusted life years gained would be negligible, which would seem to conflict with the reasoning for adopting a CEA approach. CMAs have been conducted as secondary analyses.
- The model parameter inputs are restricted to the mean values reported in the trials. There are no reported statistically significant differences between epoetin theta and epoetin beta for the main efficacy inputs considered in the models and it is possible that the small differences observed within the trials are due to random variation rather than sustained and/or meaningful differences. The data for models 1 and 2 are derived from small numbers of patients (< 30 per treatment arm). There has been no attempt to explore the impact of the distributions of the parameter values upon modelled outputs (i.e. probabilistic sensitivity analysis).

8.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

8.1 Budget impact evidence

8.1.1 Context and Methods

The budget impact analysis relates to the treatment of haemodialysis or pre-dialysis patients with anaemia due to CKD. Peritoneal dialysis patients and cancer patients receiving chemotherapy are not considered due to a reported lack of data[11]. Based on UK Renal Registry data for 2009 (ref. [26]) the company estimates there are 1,070 haemodialysis patients in Wales. Based on epidemiological data reported in the NICE clinical guideline[8], it is assumed that around 0.2% of the population have pre-dialysis severe renal disease, which equates to around 6,000 patients in Wales. Of these, around 1200 (20%) are assumed to be potentially eligible for ESA treatment. The UK Renal Registry data suggest that the net number of patients commencing haemodialysis treatment is growing at around 5.3% each year[26]. In the absence of specific data, the number of patients with pre-dialysis disease eligible for ESA treatment is assumed to grow at 5% per year[11]. Based on the above assumptions, the net number of patients eligible for ESA treatment is estimated as 2,387 in 2010, rising to 2,921 in 2014[11]. The company reports that UK Renal Registry data suggest 79% of haemodialysis patients receive ESA treatment[11] (but the report indicates this figure to be 72% for Wales[26]). It is assumed that 50% of pre-dialysis patients receive ESA treatment[11].

UK sales figures for the year to October 2009 have reportedly been used to estimate the current market share of ESAs in Wales (epoetin alfa 33%, epoetin beta 9%, darbepoetin 31%, methoxy polyethyleglycol-epoetin beta 27%)[11]. The company assumes market uptake of epoetin theta will be such that over the course of five years, 50% of short-acting ESAs (epoetin alfa and epoetin beta), and 5% of the remainder, will be switched to epoetin theta[11]. Drug costs included in the analysis are correctly based on the list prices only.

8.1.2 Results

The company-estimated annual budget impact, based on drug acquisition and administration costs, is summarised in Table 2. The company estimates that the use of epoetin theta will result in cost savings compared with the assumed current use of ESAs[11]. No sensitivity analyses have been conducted. There are a number of issues with the figures presented in Table 2 (see 7.1.3).

Table 2. Company estimates of budget impact over 5 years[11]

Product	Current total cost (2010-4)*	Market share (%)	% cost-saving with Eporatio	Likely % switch	Projected saving*
Eprex®	£9,504,000	34.6	13%	50%	£370,656
NeoRecormon®	£2,492,800	28.6	20%	50%	£149,568
Aranesp®	£8,939,000	32.5	0	5%	0
Mircera®▼	£7,862,000	4.3	0	5%	0
TOTAL 5-year saving					£520,224
* Note: these figures are uncertain – see section 7.1.3					

8.1.3 WMP critique

The budget impact estimates are based upon company derived sales figures for the ESAs discussed in 7.1. The company has provided these data, but these do not correspond with current costs reported in their submission and reproduced in Table 2. The analysis does not consider licensed biosimilar epoetin analogues, which have lower list prices than their reference products. In addition, the analysis excludes use in peritoneal dialysis and cancer patients, which may not be insignificant populations. Collectively, these issues suggest the presented budget impact analysis is subject to significant uncertainty and of unknown reliability. It should be noted that actual acquisition costs of the available ESAs may differ in practice from current list prices due to contracting arrangements.

8.2 Comparative unit costs

Table 3 includes example annual costs of relevant comparators in the maintenance phase of treatment for CKD-related anaemia, which is the indication common to all ESAs. Doses must be individualised according to Hb response; those in Table 3 are example doses that may be encountered in the maintenance phase of treatment and should not be interpreted as direct dose equivalents. Costs relate only to acquisition costs derived from BNF list prices[27].

Table 3. Example doses and costs of ESAs in the treatment of anaemia of CKD

ESA	Example maintenance dose	Annual cost of example maintenance dose (£)
Eporatio®▼	8,000–16,000 IU once weekly	2,492–4,984
Binocrit®▼	8,000–16,000 IU weekly in three divided doses	2,118–4,236
Eprex®	8,000–16,000 IU weekly in three divided doses	2,380–4,760
NeoRecormon®	8,000–16,000 IU once weekly	3,116–6,232
Aranesp®	40–80 micrograms once weekly	3,115–6,230
Mircera®▼	200 micrograms once monthly	3,594
This table does *not* imply therapeutic equivalence of drugs or the stated doses. Prices based on pre-filled syringes, no rounding of doses and no vial wastage assumed.		

9.0 ADDITIONAL INFORMATION

9.1 Shared care arrangements

- Epoetin theta treatment should be initiated by physicians experienced in the relevant indications[1].
- Epoetin theta (Eporatio®▼) is not considered suitable for shared care within NHS Wales.

9.2 Ongoing studies

The company state that there are no ongoing studies that will provide evidence relevant to ts submission in the next 6-12 months.

Patient organisation and medical expert opinion was sought.

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Appendix 1. Additional Health Economic Analysis Information

Table 1. Health economic analysis detail[11]

Base Case Model		Appropriate?
Comparator(s)	Epoetin theta (Eporatio®▼) is compared with epoetin beta (NeoRecormon®).	Epoetin beta is an appropriate comparator, but the company has not considered in its cost effectiveness analyses several other relevant ESAs that have common licensed indications and are recommended as treatment options by NICE or AWMSG: epoetin alfa (Eprex® or the biosimilar Binocrit®), darbepoetin alfa (Aranesp®), methoxy polyethylene glycol-epoetin beta (Mircera®).
Population	Five distinct populations / scenarios of use are modelled, in which all patients are assumed to be 70 kg: 1) Initiation of SC treatment in pre-dialysis renal patients. 2) Initiation of IV treatment in haemodialysis patients. 3) Maintenance SC treatment in pre-dialysis patients. 4) Maintenance IV treatment in haemodialysis patients. 5) Initiation of SC treatment in chemotherapy recipients.	Appropriate patient populations considered, although peritoneal dialysis patients are not specifically included. The company has noted that peritoneal dialysis patients were under-represented in the clinical trial programme[11].
Analysis type	CEA with secondary CMA and threshold analyses. Based on simple decisions analytic model.	The company assumes that there are potentially meaningful differences in doses received, time taken to achieve target haemoglobin levels and proportion of patients reaching target, and so presents base-case CEAs rather than CMAs. Cost utility analysis was not undertaken as the company considers that any difference in QALYs would be negligible. These would appear to be conflicting positions. The resultant cost effectiveness estimates are difficult to interpret in the context of wider healthcare decision-making, although the secondary CMAs permit comparisons with existing guidance for other ESAs. Irrespective of the analytical approach, the restriction of the comparator to epoetin beta only is a major limitation.
Perspective	Considers direct medical costs only, from the perspective of NHS Wales.	Yes.
Time Horizon	Initiation of treatment in renal disease: 16 weeks. Maintenance treatment in renal disease: 1 year. Initiation of treatment in cancer patients: 12 weeks.	Treatment is likely to be life-long in most patients with renal disease. The time horizons for initiation would seem by definition to be appropriate, but the one year time horizon may not be appropriate to capture all relevant costs and outcomes during maintenance treatment. Treatment of cancer-related anaemia is limited to 12 weeks as this is assumed to be the duration of one cycle of chemotherapy, and was the duration of treatment in the main clinical trial in this indication.
Discount rate	Not applicable due to short time horizon chosen for the analysis.	N/A

Efficacy	Efficacy parameters relate to the proportion of patients achieving haemoglobin target concentrations, withdrawal/death rates, treatment duration, and blood transfusion rates. The key active-controlled regulatory trials provide the parameter values for the five populations/scenarios that have been modelled[12-15, 18]. Efficacy data for models 3 and 4 were derived from trials of 26 weeks duration, and results have been simply extrapolated to 12 months.	The sources of the efficacy data would appear appropriate. It should be noted that only small numbers of patients (< 30 per treatment arm) provided data for models of treatment initiation in renal disease (models 1 and 2)[12, 13]. The models use the mean parameter values from the trials, none of which were statistically significantly different, and the distributions around these parameter values have not be considered. It is possible that the modelled small differences between epoetin theta and epoetin beta are chance findings rather than sustained meaningful differences. The EPAR notes that there are no clinically meaningful differences in rates of blood transfusions between epoetin theta and epoetin beta[3].
Adverse effects	Not considered in analyses.	The EPAR indicates there are small differences in treatment-emergent adverse events that are not considered clinically relevant in renal trials[3]. For the CMA scenarios, the implicit assumption is that adverse effects would be equivalent.
Utility values	Not applicable in cost effectiveness analysis.	N/A
Resource use	Relates to drug acquisition and blood transfusion costs only.	Yes.
Unit costs	Epoetin beta drug costs based on BNF list price[27], and epoetin theta cost provided by company[11]. Transfusion costs based on costs reported in literature[28], inflated to 2008/9 costs.	Yes.
Model Provided?	Yes.	-
AWMSG: All Wales Medicines Strategy Group; BNF: British National Formulary; CEA: cost effectiveness analysis; CMA: cost minimisation analysis; EPAR: European public assessment report; ESA: erythropoiesis stimulating agent; IV: intravenous; N/A: not applicable; QALY: quality adjusted life year; SC: subcutaneous.		