All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

AWMSG ADVICE PARTIALLY SUPERSEDED BY NICE GUIDANCE (TA323)

NICE GUIDANCE ISSUED NOVEMBER 2014

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Final Appraisal Report

Epoetin zeta (Retacrit®▼)

Hospira UK Ltd

Advice No: 0310 – April 2010

Recommendation of AWMSG

Epoetin zeta (Retacrit®▼) is not recommended for use within NHS Wales for the treatment of anaemia associated with chronic kidney disease, reduction of transfusion requirements in adult patients receiving chemotherapy or to increase the yield of autologous blood from patients in a predonation programme. The case for cost effectiveness of epoetin zeta (Retacrit®▼) has not been proven.

This report should be cited as:

All Wales Medicines Strategy Group Final Appraisal Report
Epoetin zeta (Retacrit®▼) – April 2010

ABBREVIATIONS

AWMSG	All Wales Medicines Strategy Group
BNF	British National Formulary
CI	Confidence interval
CKD	Chronic kidney disease
CRF	Chronic renal failure
CMA	Cost minimisation analysis
EC	European commission
EMEA	European Medicines Agency
EPAR	European Public Assessment Report
EPO	Erythropoietin
ESA	Erythropoiesis stimulating agent
HD	Haemodialysis
IV	Intravenous
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
PRCA	Pure Red Cell Aplasia
RMP	Risk Management Plan
SC	Subcutaneous
SPC	Summary of Product Characteristics
WMP	Welsh Medicines Partnership

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 28th April 2010

The recommendation of AWMSG is:

Epoetin zeta (Retacrit®▼) is not recommended for use within NHS Wales for the treatment of anaemia associated with chronic kidney disease, reduction of transfusion requirements in adult patients receiving chemotherapy or to increase the yield of autologous blood from patients in a predonation programme. The case for cost effectiveness of epoetin zeta (Retacrit®▼) has not been proven

Key factor influencing the recommendation:

- There are several uncertainties and limitations in the economic model provided in the company's submission.

2.0 PRODUCT DETAILS

2.1 Licensed indication

Epoetin zeta (Retacrit®▼) is licensed for use:

- in the treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult and paediatric patients including:
  - Anaemia associated with chronic renal failure in adult and paediatric patients on haemodialysis and adult patients on peritoneal dialysis.
  - Severe anaemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing dialysis.
- in the treatment of anaemia and reduction of transfusion requirements in adult patients 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).
- to increase the yield of autologous blood from patients in a predonation programme. Its use in this indication must be balanced against the reported risk of thromboembolic events. Treatment should only be given to patients with moderate anaemia (no iron deficiency), if blood saving procedures are not available or insufficient when the scheduled major elective surgery requires a large volume of blood (four or more units of blood for females or five or more units for males)[1].

The company have limited their submission to the management of symptomatic anaemia of chronic kidney disease (CKD).

2.2 Dosing

For adult patients on haemodialysis, treatment is divided into two stages:

1. Correction phase: 50 IU/kg three times per week by the intravenous route (IV). When a dose adjustment is necessary, this should be done in steps of at least four weeks. At each step, the increase or reduction in dose should be of 25 IU/kg three times per week.
2. Maintenance phase: Dose adjustment in order to maintain haemoglobin values at the desired level: haemoglobin between 10 and 12 g/dL (6.2 to 7.5mmol/L). The recommended total weekly dose is between 75 and 300 IU/kg by the intravenous route.

Dosing schedules for the other indications (and patient groups) can be found in the summary of product characteristics (SPC)[1].

2.3 Market authorisation date

18 December 2007[2]

2.4 UK Launch date

March 2008[2]

3.0 DECISION CONTEXT

3.1 Background

Anaemia is a common complication in patients with chronic renal failure, and although its pathogenesis is multifactorial, the loss of peritubular cells in the kidney responsible for the synthesis and secretion of erythropoietin (EPO) is considered the key etiologic factor[3]. The main impact of anaemia on organ function is reduced oxygen delivery to tissues leading to debilitating symptoms such as: fatigue, exercise intolerance,

impaired cognitive function, sleep disorder, altered haemostasis, and depressed immune function[3]. Anaemia is also associated with a high prevalence of cardiovascular disease in renal patients, and their consequent increased morbidity and mortality[3]. It has been reported that cardiovascular disease accounts for more than 50% of deaths in these patients[3].

Exogenous replacement therapy of EPO by recombinant hormone epoetin is a well accepted therapy for the treatment of anaemia in patients with CKD and is reported to be effective in about 90-95% of such patients[3]. Current NICE guidance specifically on anaemia management in CKD recommends that the management of anaemia should be considered if the haemoglobin is ≤11g/dL (or 10g/dL if under two years of age)[4]. Treatment should be aimed to maintain stable haemoglobin levels between 10.5 and 12.5g/dL for adults and children older than two years of age[4].

For market authorisation, the EMEA requires that biosimilar EPOs are assessed in at least two adequately powered randomised parallel group trials versus the reference product. Sensitivity to EPO is higher in EPO-deficiency states so patients with renal anaemia are recommended as the target population and trials should include a correction and maintenance phase. Patient populations should not be mixed as target haemoglobin levels differ between dialysis and pre-dialysis patients and ideally clinical comparability should include both routes of administration (IV and subcutaneous [SC])[5]. The company have submitted clinical data to WMP based on the information provided to the EMEA for market authorisation i.e. in patients with renal anaemia requiring haemodialysis.

The company estimates that approximately 790 patients are receiving dialysis (peritoneal or haemodialysis) and erythropoiesis stimulating agents in Wales; this is based on English prevalence data and mid 2006 Welsh population figures[2] (refer also to section 8).

3.2 Comparators

Short-acting:

- Epoetin alfa (Eprex®, Binocrit®▼)
- Epoetin beta (NeoRecormon®)

Longer-acting:

- Darbepoetin alfa (Aranesp®)
- Methoxy polyethylene glycol-epoetin beta (Mircera®▼)

The original recombinant human EPOs (epoetin alfa and epoetin beta) have now been in clinical use for nearly 20 years[6-8]. Other biosimilar products have recently become available (e.g. epoetin alfa [Binocrit®▼][9] and epoetin zeta [Retacrit®▼])[1]. These have a relatively short acting circulating half-life and require two or three injections per week. Longer acting erythropoiesis stimulating agents (ESAs) include darbepoetin alfa (Aranesp®)[10] and methoxy polyethylene glycol-epoetin beta (Mircera®▼)[11],allowing less frequent dosing regimens of once every two weeks, and in some cases once monthly. NICE guidance recommends that the choice of ESA should be dependent on the patient's dialysis status, the most appropriate route and frequency of administration, and the local availability and cost[4]. Not all of the EPOs currently available however were included in the NICE guideline as they were not licensed at the time.

3.3 Guidance and related advice

- NICE: Anaemia management in people with chronic kidney disease (CG39)[4]
- NICE: Early identification and management of CKD in adults in primary and secondary care (CG73)[12]
- UK Renal Association: Clinical Practice Guideline 4th ed (2007)[13]

- National Collaborating Centre for Chronic Conditions, Royal College of Physicians: Guideline of anaemia management in CKD (2006)[14]
- Joint speciality committee on renal medicine of the Royal College of Physicians and the Renal Association: UK guidelines for identification, management and referral of CKD in adults (2006)[15]
- Scottish Intercollegiate Guidelines Network (SIGN): Diagnosis and management of CKD (2008)[16]

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The company submission is based on two pivotal trials for the treatment of renal anaemia in patients on haemodialysis during the correction and maintenance phase. Both studies were compared against epoetin alfa (reference product) and indicated that both products were clinically equivalent in terms of surrogate endpoints (haemoglobin and haematocrit concentrations). Some dosage adjustment was required when transferring between the two products though this was not significantly different. No additional adverse effects were noted during the trials though data are limited and this will be addressed by the risk management plan. Due to a lack of data on SC use, epoetin zeta is currently licensed for IV use only in renal anaemia; this differs to some of the other available ESAs on the market. The manufacturer of epoetin zeta are currently seeking market authorisation for SC use.

4.2 Review of the evidence on cost-effectiveness

A cost minimisation analysis (CMA) of epoetin zeta compared against epoetin alfa, epoetin beta and darbepoetin has been conducted on the basis of equivalent efficacy and assumed equivalence in other dimensions of health outcome.

The company concludes that epoetin zeta is less costly than epoetin alfa in the maintenance phase of treatment when administration costs are incorporated. However, the analysis in haemodialysis patients appears biased in favour of epoetin zeta due to the assumptions of once weekly administration for epoetin zeta and thrice weekly administration for epoetin alfa. When both are administered at the same frequency, epoetin alfa remains the least costly, albeit that the actual cost differences between these two ESAs in the haemodialysis setting are small (<£2/week).

The ESA costs assumed in the analysis are based on the entire dose ranges listed in the respective SPCs. This may not reflect the usual doses and costs of ESAs in practice, where the use of the extreme maximum doses, as listed in the SPCs, may not be typical. This limits the extent to which the doses and costs provided in the analysis are directly comparable. The CMA appropriately uses list prices for estimating costs, although it should be noted that actual acquisition costs may differ depending on contracting arrangements.

4.3 Limitations of the evidence

- There is a lack of data for the use of epoetin zeta in paediatrics, peritoneal dialysis patients, patients not yet on dialysis and administration via the SC route.
- The pivotal trials did not consider direct health outcomes such as quality of life or mortality.

5.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

5.1 Clinical evidence

The company have submitted data on two randomised, double-blind, multicentre phase III equivalence trials comparing the use of epoetin zeta with epoetin alfa (reference product) in patients with CKD on haemodialysis. The first of these trials evaluated the use of epoetin zeta for the correction of haemoglobin concentration and the second for maintenance of haemoglobin concentrations[17,18].

In the correction study (n=609) the two primary efficacy endpoints were met for equivalence. Based on the per protocol group (n=541), the mean weekly dosage of epoetin per kg body weight during the last four weeks of treatment was 182.20IU/kg/week for epoetin zeta versus 166.14IU/kg/week for epoetin alfa. Though the dosage of epoetin zeta was around 10% higher than epoetin alfa, the 95% confidence interval (CI) of the mean (test-reference) difference fell within the revised (EMEA-approved) equivalence range of 45IU/kg/week. The mean haemoglobin level during the last four weeks of treatment was 11.61g/dL for epoetin zeta versus 11.63g/dL for epoetin alfa. The difference was within the predefined equivalence range of ± 1.0g/dL[17]. Additional secondary endpoints are included in Appendix 1, Table 1A.

In the maintenance study (n=313) all patients were initially prescribed epoetin alfa during the run-in phase of the trial which lasted for 12 to 18 weeks, ensuring that patients entering the double-blind phase of the trial were already at their target haemoglobin level of between 10.5 and 12.5g/dL and hence eligible for study inclusion. The double-blind phase of the trial had a cross-over design so that after 12 weeks of either epoetin zeta or epoetin alfa, patients were then changed to the alternative product. Again the trial had two primary end-points. The mean weekly EPO dosage over the double-blind period was 92.68IU/kg/week for epoetin zeta and 92.58IU/kg/week for epoetin alfa. The 95% CI of the difference fell within the equivalence range of ± 45IU/kg/week. A minor dose increase was required when switching from epoetin alfa to epoetin zeta due to variations in bioactivity[19]. The mean haemoglobin level over the double-blind period was 11.35g/dL for epoetin zeta and 11.54g/dL for epoetin alfa. The 95% CI of the difference of the mean haemoglobin was within the predefined equivalence range of ± 0.6g/dL[21]. Additional secondary endpoints are included in Appendix 1, Table 1B.

Patients from both sets of trials were eligible for entry into an open label uncontrolled safety trial where all patients (n=745) received epoetin zeta. Results from this trial are considered within Appendix 1, Table 1C and in the safety section of this report. Overall data suggested that adequate haemoglobin levels were maintained and that there was no loss of efficacy over the course of the study (additional 28 weeks, up to an additional 80 weeks in a sub-population)[20].

5.2 Safety

No new adverse reactions were identified from the clinical trials and the safety profile of epoetin zeta would appear to be comparable to other epoetin products. In the open label extension study the majority of adverse effects included 'infections, infestations' and 'gastrointestinal disorders'[20].

As pre-marketing data are limited, the company have been asked to complete a SC study using epoetin alfa as the reference product as part of the risk management plan (RMP). The RMP also includes post-marketing investigations on the risk of neutralising antibody formation, thromboembolic events and monitoring of CNS events including hypertensive encephalopathy[19].

Eleven patients in the correction study and three patients in the maintenance study tested positive at baseline for non-neutralising anti-EPO antibodies. No additional patients developed antibodies during the studies and there were no cases of pure red cell aplasia (PRCA) in these studies or during the open label extension study[17,18,20].

The EMEA has recently reviewed the safety of EPOs as a result of data indicating that treatment of anaemia associated with cancer has been associated with an excess mortality and treatment of anaemia in CKD to a relatively high target haemoglobin level has been associated with an increased risk of mortality and cardiovascular morbidity. The EMEA concluded that the benefits of treatment outweigh the risks but have suggested the following changes to the product information[22]:

- Changes to the 'Indication' section, stating that epoetins should be used in the treatment of anaemia only if associated with symptoms.
- Changes to the 'Posology' section, stipulating a uniform target haemoglobin range for all EPOs of 10 to 12g/dL with a warning not to exceed a concentration of 12g/dL.
- Changes to the 'Special Warnings and Precautions for Use' section, adding an explanation that trials have shown a small unexplained excess mortality in association with high-target haemoglobin concentrations and they have not shown significant benefits attributable to the administration of EPOs to increase haemoglobin concentration beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.
- Changes to the 'Pharmacodynamic Properties' section, to include new information on results of clinical trials, which have shown excess mortality in patients who have anaemia associated with various common cancers who received EPOs compared with those who did not.

The EMEA recommend that healthcare professionals should use EPOs in accordance with their approved indication and dosing[22].

6.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- At the time of the trials SC epoetin alfa was temporarily contra-indicated in renal anaemia due to concerns over immunogenicity, therefore comparison between epoetin zeta and the reference product was not possible[19]. As the immunogenicity of SC epoetin zeta has not been evaluated in patients with renal anaemia at risk of antibody-induced PRCA, a respective warning and restriction to IV use in this population has been included into the SPC[1,19]. However some of the other EPOs may be used SC in renal anaemia[7,10,11]. The manufacturer of epoetin zeta are currently seeking market authorisation for SC use.
- Minor dosage adjustments are required when switching from epoetin alfa to epoetin zeta to maintain steady haemoglobin levels; in clinical trials this constituted a 10% increase in dose.
- Consequently when switching from epoetin zeta to epoetin alfa, the dose was decreased by approximately 10% in the maintenance study. This was due to a 10% increase in haemoglobin level[19].
- Though a difference in dose was noted in the clinical trials it was within the pre-defined equivalence range.
- It is unclear why there was a difference in the pre-specified equivalence range for haemoglobin between studies, though both trials would have met the stricter endpoint of ± 0.6g/dL[17,18].

- No data have been presented by the company for the use of epoetin zeta in paediatrics, peritoneal dialysis patients, and patients not yet on dialysis or on administration via the SC route.
- No quality of life data has been provided for the use of epoetin zeta in renal anaemia.
- The main outcomes of the pivotal studies were presented as surrogate endpoints; no mortality data has been provided.

7.0 REVIEW OF HEALTH ECONOMIC EVIDENCE

7.1 Context

The company submission[2] provides brief details of a cost minimisation analysis (CMA) of epoetin zeta compared against other available ESAs for the management of symptomatic anaemia associated with CKD. The analysis excludes methoxy polyethylene glycol beta (Mircera®▼), which has been recommended by AWMSG as a treatment option in Wales[23]. The analysis relates to an adult patient weighing 70kg. An economic analysis has not been provided specifically for the use of epoetin zeta in paediatric patients or in patients meeting the other licensed indications.

7.2 Methods

Modelling approach: The basis for the cost minimisation approach is that epoetin zeta has been demonstrated in two phase III trials[17,18] to be equivalent to the reference agent (epoetin alfa) in terms of achieving and maintaining target haemoglobin levels and epoetin dose[19]. Additionally, reference is made to the 2006 NICE clinical guideline on the management of anaemia in CKD, which considered there to be no evidence to distinguish between ESAs (epoetin alfa, epoetin beta and darbepoetin) in terms of efficacy[4]. The Company assumes this to mean that ESAs produce equivalent health outcomes in terms of efficacy and safety.

The analysis provides the weekly costs of ESAs from the perspective of NHS Wales.

Inputs: The only inputs are the acquisition and administration costs of epoetin zeta, epoetin alfa, epoetin beta and darbepoetin. In the main analysis, acquisition costs are reported to be based on the mean costs per unit (IU) of epoetin for each of the ESAs, as listed in the current British National Formulary (BNF)[24], and the licensed doses of each of the ESAs as applicable to a 70kg patient. Darbepoetin IU/kg doses have been estimated, based on conversion factors presented in its SPC[10]. Administration costs per dose of ESA have been derived from a Health Technology Assessment of ESAs in the management of anaemia associated with cancer published in 2007[25] and inflated to current prices.

In an additional analysis, the acquisition costs are based on standardised approach to dosing, reportedly based on company-sought expert opinion. In this approach, all patients are assumed to receive a total weekly epoetin dose of 4000IU to 6000IU, with epoetin zeta, epoetin alfa and epoetin beta given as a once or twice weekly regimen and darbepoetin given once weekly or once fortnightly. The company considers that this standardised approach to dosing is for ESA-naive patients in the pre-dialysis phase (i.e. via subcutaneous injection) and is not applicable to the current decision problem. It should be noted that, in the treatment of anaemia associated with CKD, epoetin zeta is only licensed for IV administration[1]. Results of this additional analysis are presented in Table 2B, Appendix 2.

7.3 Results

The results of the main analysis, including administration costs, as presented in the company submission are displayed in Table 1. The company submission claims the

cost of epoetin zeta is lower than that of epoetin alfa when considering costs beyond one week. However, there are some issues which cast doubt on this claim in relation to haemodialysis patients, as discussed in section 7.4. As the analysis uses the minimum and maximum SPC-recommended doses to provide a range of costs for the base case analysis, no further sensitivity analyses have been conducted.

Table 1. ESA weekly treatment costs for 70kg patient

ESA	Weekly dose - correction	Weekly dose - maintenance	Weekly cost (£) - correction	Weekly cost (£) - maintenance
Epoetin zeta – HD†	10,500 IU	5,250−21,000 IU	84.24	37.98 – 127.07*
Epoetin zeta – PD†	7,000 IU	3,500−7,000 IU	56.16	36.36 – 56.16
Epoetin zeta – ND†	10,500 IU	3,570−6,930 IU	84.24	45.03 – 64.04
Epoetin alfa	10,500 IU	5,250−21,000 IU	83.38	54.11 – 141.92
Epoetin beta	4,200 IU to a maximum 50,400 IU		56.30 to a maximum 402.40	
Darbepoetin alfa	6,300 IU per week or 10,500 IU every 2 weeks		57.82 or 45.42 (weekly pro rata cost)	

HD=haemodialysis patients; PD=peritoneal dialysis patients; ND=non-dialysis patients

*NB: is based on once weekly administration, rather than thrice weekly administration assumed for epoetin alfa

†Epoetin zeta is licensed only for intravenous administration in these patients

7.4 WMP critique of the company's economic evidence

- The company's claim that treatment with epoetin zeta is less costly than with epoetin alfa appears subject to some uncertainty in the haemodialysis setting. The total weekly maintenance dose for epoetin alfa is assumed to be divided into three administrations per week and attracts the costs of three administrations per week. However, the total weekly maintenance dose of epoetin zeta is assumed to be given in one single dose, which attracts the cost of only one administration. Although the SPC for epoetin zeta states the recommended total weekly dose is between 75 and 300 IU/kg[1], this does not specifically state that the dose should be given once weekly. This is also the case for epoetin alfa[6]. The BNF indicates that the weekly maintenance dose of epoetin alfa (which is the same weekly dose as for epoetin zeta in the haemodialysis setting) may be given as a single dose or in divided doses[24]. For epoetin zeta, the BNF indicates that the weekly maintenance dose is usually given in three divided doses[24]. It is also noteworthy that the pivotal phase III maintenance trial permitted both epoetin alfa and epoetin zeta to be administered once to three times per week[18], rather than specifying epoetin alfa be administered more frequently than epoetin zeta. The assumption by the company that epoetin alfa would be administered three times more frequently than epoetin zeta would appear to bias the analysis in favour of epoetin zeta. Based on the company estimates of costs/IU, when each are assumed to be given in the same number of doses per week, epoetin alfa remains the less expensive of the two ESAs during both the correction and the maintenance phases of treatment in the haemodialysis setting, albeit that the actual cost differences are small (<£2/week).
- In peritoneal dialysis and non-dialysis patients, epoetin zeta may offer lower costs than the comparator epoetins, but this will depend on the actual doses received by patients. It should be noted that epoetin zeta is not licensed for subcutaneous administration in the treatment of anaemia associated with CKD[1],

in contrast to epoetin alfa[6], epoetin beta[7] and darbepoetin[10]. Subcutaneous administration may be the preferred route for patients who are not receiving haemodialysis to avoid the puncture of peripheral veins[6,7,10].

- There appear to be some inconsistencies in the costs/IU presented in the company submission and those that can be calculated from the BNF, which marginally biases the analysis against darbepoetin. The approach of costing ESAs based on mean IU costs does not consider any wastage that may occur from the use of prefilled syringes, although WMP-sought expert opinion is that, in practice, doses may be rounded up or down to avoid vial wastage.
- It should be noted that the period for correction of haemoglobin levels may exceed one week, (WMP-sought expert opinion indicates that Hb correction may take three months or more for a patient commencing treatment), and so the assertion in the company submission that only the first week of treatment with epoetin zeta would be more expensive than with epoetin alfa would seem uncertain.
- The approach of costing ESA doses based on the entire dose ranges listed in the SPC may not reflect the usual doses and costs of ESAs in practice, where the use of the extreme maximum doses listed in the SPCs may not be typical. This limits the extent to which the doses and costs provided in Table 1 are directly comparable.
- It should also be noted that actual acquisition costs may differ in practice from those based on list prices due to contracting arrangements.

7.5 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost effectiveness of epoetin zeta in the treatment of symptomatic anaemia in patients with CKD.

8.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

8.1 Methods

The NICE costing report for the 2006 clinical guideline on managing anaemia for people with CKD[4] estimates the number of haemodialysis, peritoneal dialysis and non-dialysis patients with CKD in England who are currently receiving ESAs for the management of anaemia. Mid 2006 population data for England and Wales have been used to estimate the equivalent number of patients in Wales, and it is assumed that the prevalence rates remain constant over time. Projected increases in population sizes are used to estimate eligible patient numbers over a five year period.

The weekly maximum and minimum acquisition costs for the maintenance phase of treatment, as presented in the economic analysis, Section 7 Table 1, are used to estimate the annual budget impact of the introduction of epoetin zeta[2]. The company notes that costs in the correction phase of treatment would be different to those in the maintenance phase of treatment, but considers this to be negligible. It is assumed that the ESA market is currently split evenly between the three ESAs epoetin alfa, epoetin beta and darbepoetin. The range of cost saving based on the maximum and minimum costs of ESAs are presented for haemodialysis, peritoneal and non-dialysis patients based on scenarios of 100%, 25% and 0% market share for epoetin zeta[2].

8.2 Results

The annual budget impact as estimated by the company for years 1 and 5 is summarised in Table 2. The company estimates that the use of epoetin zeta will result in cost savings compared with the assumed current use of ESAs, which are similar in each of the next five years[2].

8.3 Critique

There are a number of limitations to the budget impact estimates presented in the company submission, which warrants cautious interpretation. The estimates are based upon the drug acquisition and administration costs presented in Section 7 Table 1. These appear biased in favour of epoetin zeta due to the assumption of once weekly administration for epoetin zeta compared with thrice weekly administration for epoetin alfa, as discussed in section 7.4. In addition, the approach to estimating the range of costs of ESAs based on the maximum and minimum stated doses in the SPCs of the respective ESAs is likely to have produced cost estimates that are unrepresentative of costs typically seen in practice. This will result in the estimated cost savings being subject to significant uncertainty.

A further source of uncertainty is introduced by the use of the prevalence figures quoted in the 2006 NICE costing report. The NICE costing report indicated that the number of non-dialysis patients eligible for ESAs was likely to increase as a result of the NICE guidance, but this is not considered in the company submission. The assumption of constant prevalence rates is also uncertain.

As in the economic analysis, methoxy polyethylene glycol beta (Mircera®▼) is not considered in the budget impact analysis. The assumed equal split between epoetin alfa, epoetin beta and darbepoetin may not be representative of the current ESA market as a whole, or across the haemodialysis, peritoneal dialysis and non-dialysis markets. It should also be noted that actual acquisition costs may differ in practice from those based on list prices due to contracting arrangements.

Table 2. Annual budget impact estimated over 5 years

Year	1	5
Haemodialysis patients		
Patient numbers	637	650
Estimated cost of current use of ESAs (min to max), no epoetin zeta use	£1.72m to £6.65m	£1.76m to £6.78m
100% uptake of epoetin zeta, no use of other ESAs	Saving: £0.46m to £2.43m	Saving: £0.47m to £2.49m
25% uptake of epoetin zeta, 75% use of other ESAs	Saving: £0.12m to £0.61m	Saving: £0.12m to £0.62m
Peritoneal dialysis patients		
Patient numbers	172	175
Estimated cost of current use of ESAs (min to max), no epoetin zeta use	£0.46m to £1.80m	£0.47m to £1.83m
100% uptake of epoetin zeta, no use of other ESAs	Saving: £0.14m to £1.29m	Saving: £0.14m to £1.32m
25% uptake of epoetin zeta, 75% use of other ESAs	Saving: £0.03m to £0.32m	Saving: £0.04m to £0.33m
Non-dialysis patients		
Patient numbers	386	394
Estimated cost of current use of ESAs (min to max), no epoetin zeta use	£1.04m to £4.02m	£1.06m to £4.11m
100% uptake of epoetin zeta, no use of other ESAs	Saving: £0.14m to £2.74m	Saving: £0.14m to £2.80m
25% uptake of epoetin zeta, 75% use of other ESAs	Saving: £0.03m to £0.68m	Saving: £0.04m to £0.70m

8.4 Comparative unit costs

Table 1 in section 7 provides comparative weekly costs, including administration costs, as estimated by the company. It should be noted that, in the haemodialysis setting, the weekly costs in the maintenance phase of treatment with epoetin zeta would be £54.54 to £143.63 if thrice weekly administration, rather than once weekly administration, is assumed.

The company submission does not consider methoxy polyethylene glycol beta (Mircera®▼), which is given monthly in patients whose haemoglobin concentration has stabilised. For comparison, the BNF list cost of methoxy polyethylene glycol beta 200micrograms/month is £299.54[24]. Including the assumed cost per dose administration used in the economic analysis (£8.28)[2], the pro rata weekly cost would be £76.96.

9.0 ADDITIONAL INFORMATION

9.1 Shared care arrangements

- Epoetin zeta (Retacrit®▼) is not suitable for shared care within NHS Wales.

9.2 Previous AWMSG advice

- Methoxy polyethylene glycol-epoetin beta (Mircera®▼) was recommended in October 2009 as an option for use within NHS Wales for the treatment of adults with symptomatic anaemia associated with chronic kidney disease[23].
- Epoetin delta (Dynepo®) was originally recommended in February 2008 for use in patients on dialysis (and in patients not on dialysis) within NHS Wales for the treatment of anaemia associated with chronic renal failure[26]. In March 2009 the European Commission (EC) issued a decision to withdraw the marketing authorisation for Dynepo® (epoetin delta). This decision follows a letter from the marketing authorisation holder (MAH) responsible for Dynepo® (Shire Pharmaceutical Contract Limited) informing the EC that the company had decided to voluntarily withdraw the marketing authorisation for commercial reasons[27].

9.3 Previous NICE advice

Refer to section 3.3

9.4 Ongoing studies

- Post-authorisation cohort study of epoetin zeta for the treatment of renal anaemia[2].
- Phase III trial of SC epoetin zeta for the treatment of anaemia associated with CKD is currently in progress[2].

9.5 Other

- The UK Renal Registry (established by the Renal Association) provides a focus for the collection and analysis of data on the incidence, clinical management and outcome of renal disease. Currently there is a concentration of data concerning renal replacement therapy, including transplantation, but the Registry will extend to other forms of treatment of renal disease in the future. It is considered a source of comparative data, for audit/benchmarking, planning, clinical governance and research; providing data for bodies such as NHS Trusts, and commissioning authorities[28].
- The Pharmacovigilance working party (PhVWP) of the EMEA has recommended that the product information for all epoetins includes a

request that the trade name of the epoetin used is recorded in the patient notes. This will be used to aid assessment of cases of PRCA in relation to any quality specifications of an individual epoetin. This request was transmitted to the reference member state for Eprex® and the CHMP for all other epoetins[29].

9.6 Patient organisation information

A patient organisation submission was not received.

9.7 Medical expert summary

Medical expert opinion was provided to members.

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Appendix 1. Additional Clinical Information

Table 1A. Prospective study of epoetin zeta in anaemia: Correction-phase trial in haemodialysis patients

Ref	Study type	No. patients	Inclusion/ exclusion criteria	Baseline characteristics	Treatment regimens	Outcomes (epoetin zeta versus epoetin alfa)
CT-830-04-0003[17]	RCT, DB, multicentre, PIII 37 European centres (no UK centres) Open run-in period of up to six weeks 1:1 randomisation 24 weeks DB phase Permitted entry into 28 week OLE study (epoetin zeta follow-up safety trial)	609 randomised epoetin zeta: n=305 Epoetin alfa: n=304 (safety population) Treated for at least four weeks (FAS): epoetin zeta: n = 300, epoetin alfa: n = 298 Completed treatment without major protocol deviations (PP): epoetin zeta: n =273, epoetin alfa: n = 268	Inclusion: • Aged 18-75 years • HD with ESRD • Baseline Hb <9g/dL despite optimal iron supplementation Exclusion • Other cause of anaemia • Current malignancy • CRP>10mg/dL • Epilepsy • Uncontrolled hypertension • Severe disease within last six months • Detectable neutralising anti-EPO antibodies	• 58% male • Mean age: 53 years • Time since ESRD: 24-26 years • Mean Hb: 8g/dL • Mean HCT: 25% Diagnosis leading to RF: • Approx 10% diabetic neuropathy • Approx 20% hypertensive nephropathy • Approx 30% glomerulo-nephritis • Approx 40% other reason/ missing Data based on safety population. Figures have been rounded for convenience	Epoetin zeta or epoetin alfa Starting doses: Epoetin naïve: 50IU/kg IV tiw Epoetin-experienced: 75IU/kg/week (IV) higher than their pre-trial dose Dosing titrated to achieve target Hb of 11 to 12g/dL Maximum dose 200IU/kg tiw	**Primary endpoints (PP):** Mean weekly dosage of epoetin/kg body weight during last 4 weeks of treatment: 182.20 ± 118.11 versus 166.14 ± 109.85IU/kg/week (95% CI: -3.21 to 35.34 IU/kg/week). Values within range of ± 45IU/kg/week. Mean Hb levels during last 4 weeks of treatment: 11.61 ± 1.27 versus 11.63 ± 1.37g/dL (95% CI: -0.25 to 0.20g/dL). CI within predefined equivalence range of ± 1g/dL. **Secondary endpoints (PP):** Proportion of patients with treatment success*: 84.2% versus 85.8%; p=0.63 Proportion of patients with maintenance success†: 86.4% versus 84.7% (95% CI: -4.2 to 7.7; p=0.63) Increase of Hb over time: 8.07 ± 0.79g/dL to 11.60 ± 1.37g/dL versus 8.04 ± 0.79g/dL to 11.61 ± 1.44g/dL; p=0.85 Proportion of patients with an increase of Hb >1g/dL for 4 weeks:98.9% versus 99%, p=NS Percentage Hb measurements >10g/dL: 64.3 ± 24.0% versus 65.7 ± 23.7% Percentage HCT measurements >30%: 68.6 ± 22.9% versus 69.7 ± 22.0% Proportion of patients requiring one or more blood transfusions: 3.66% versus 4.85%, p=NS Mean weekly dosage of epoetin/kg body weight during each interval of 4 weeks of treatment: p=NS Mean Hb and HCT levels during each interval of 4 weeks of treatment: p=NS

Table 1B. Prospective study of epoetin zeta in anaemia: Maintenance-phase trial in haemodialysis patients

Ref	Study type	No. patients	Inclusion/ exclusion criteria	Baseline characteristics	Treatment regimens	Outcomes (epoetin zeta versus epoetin alfa)
CT-830-04-0002[18]	RCT, DB, cross-over, multicentre, PIII 39 European centres (no UK centres) Two phases: Open label epoetin alfa for 12 to 18 weeks (to meet criteria for DB phase) DB phase: 12 weeks of one product then switched to alternative product for further 12 weeks. Permitted entry into 28 week OLE study (epoetin zeta follow-up safety trial)	313 randomised epoetin zeta: n=155 Epoetin alfa: n=158 (safety population) Treated for at least four weeks (FAS): epoetin zeta: n=143, epoetin alfa n=139 Completed treatment without major protocol deviations (PP): N=239 Initial treatment with epoetin zeta: n=121, initial treatment with epoetin alfa: n=118	Inclusion: • Aged 18 to 75 years • HD patient with ESRF and renal anaemia currently on epoetin treatment for at least three months • On stable, adequate dialysis for at least three months To meet randomisation criteria for DB phase: Target Hb of 10.5 to 12.5g/dL with constant epoetin alfa dosage and no intra-individual change in Hb that exceeded 0.6g/dL over four weeks. Exclusion criteria: As above	• 60.1% male • Median age: 57 years (20 to 77) • Median Hb: 11.6g/dL (7.5 to 15.1) • Median HCT 35% (25.9 to 41) • Median time since ESRF: 37 years Diagnosis leading to RF: • 16.7% diabetic neuropathy • 7.5 % hypertensive nephropathy • 34.6% glomerulo-nephritis • 43.4% other reason/ missing Data based on safety population.	Epoetin alfa or epoetin zeta IV one to three times a week. Dose adjustment according to Hb levels and only in patients with optimal iron status.	**Primary endpoints (PP):** Intra-individual change (test-reference) in mean weekly dosage per kg body weight of each product during DB treatment period: 92.68 (12.74 to 398.41) versus 92.58 (10.53 to 393.07) IU/kg/week (95% CI: -4.67 to 4.29IU/kg/week). Within predefined equivalence rage of ± 45IU/kg/week Intra-individual change (test reference) in mean Hb level during DB treatment with each study drug: 11.35 (8.96 to 14.22) versus 11.54 (8.74 to 13.84) g/dL (95% CI: 0.09 to 0.28g/dL). Within predefined equivalence range of ±0.6g/dL **Secondary endpoints (PP):** Mean HCT levels during DB treatment with each study drug: 34.30 ±2.52% versus 34.87 ±2.15% (95% CI: 0.28 to 0.85) Proportion of patients with any permanent changes of Hb levels of >1g/dL during DB period: 10.5% versus 11.3%; p=NS Proportion of patients with any transient changes of Hb levels of >1g/dL during DB period: 55.2% versus 56.1%; p=NS Proportion of patients with any permanent dose change during DB period: 39.3% versus 41.0%; p=NS Proportion of patients with any transient dose change during DB period: 59.0% versus 64.9%; p=NS Proportion of patients with any Hb measurement outside target range (10.5 to 12.5g/dL) during DB period: 67.4% versus 63.6%, p=NS Incidence of blood transfusions: 1.3% versus 0.8%; p=NS

Table 1C. Prospective study of epoetin zeta in anaemia: Open label extension safety trial in haemodialysis patients

Ref	Study type	No. patients	Inclusion/ exclusion criteria	Baseline characteristics	Treatment regimens	Outcomes (epoetin zeta)
CT-830-04-004[20]	OLE, uncontrolled, multicenter, PIII trial 56 weeks study duration (Bulgarian group 108 weeks)	745 enrolled 532 completed 56 week study 123/164 Bulgarian patients completed 108 weeks	Inclusion: • HD patients who had completed DB treatment phase of trials 0002 and 0003. Exclusion: • Evidence of myelodysplastic syndrome • Detectable neutralising anti-EPO antibodies • malignancy	Not supplied.	Epoetin zeta IV one to three times a week Maximum dose 200IU/kg tiw	**Primary endpoints:** No patients developed neutralising antibodies Most commonly reports adverse effects were infections and infestations (34.1%), injury, poisoning and procedural complications (25.8%) and gastrointestinal disorders (21.9%). **Secondary endpoints:** Mean weekly epoetin dosage: 140 IU/kg/week (170IU/kg/week in Bulgarian patients) Mean Hb levels/week: 11.3 to 11.6g/dL (11.1 to 11.6g/dL for Bulgarian patients) Mean HCT levels: 33.7% to 35.2% Permanent changes in Hb levels > 1g/dL: 70.9% Transient changes in Hb levels > 1g/dL: 88.6% Hb measurements outside target range (10.5 to 12.5g/dL): 90.2% Permanent dose change: 88.32% (minor changes) Transient dose change: 95.7% (minor changes) Incidence of blood transfusions: 7.2% required one or more.

CI: confidence interval; CRP: C-reactive protein; DB: double-blind; EPO: erythropoietin; ESRD: end-stage renal disease; ESRF: end-stage renal failure; FAS: full analysis set; Hb: haemoglobin; HCT: haematocrit; HD: haemodialysis; IU: international units; IV: intravenous; LOCF: last observation carried forward; NS: non-significant; PP: per protocol; OLE: open label extension; RCT: randomised controlled trial; RF: renal failure; SC: subcutaneous; tiw: three times a week

*Hb concentration ≥11.0g/dL for two consecutive weeks without any blood transfusion within the preceding three months
† maintenance of mean Hb concentration of 11.0 ± 1.0g/dL for at least four consecutive weeks
§ deep vein thrombosis requiring anticoagulant treatment, pulmonary embolism, myocardial infarction, cerebral ischemia, left ventricular failure, thrombotic microangiopathy within 12 weeks of treatment with epoetin zeta

Appendix 2. Additional Health Economic Information

Table 2A. Health economic analysis detail[1]

Base Case Model		Appropriate?
Comparator(s)	Epoetin zeta is compared against epoetin alfa, epoetin beta and darbepoetin.	The ESAs considered in the analysis are appropriate comparators; however, the analysis fails to consider methoxy polyethylene glycol beta (Mircera®▼) which has recently been recommended by AWMSG as a treatment option in Wales[23]
Population	Analysis relates to 70kg adult with anaemia due to CKD	Restricted submission
Analysis type	Simple cost minimisation analysis (CMA)	NICE considered there to be no evidence to distinguish between the ESAs epoetin alfa, epoetin beta and darbepoetin in terms of efficacy, which the company assumes to mean that outcomes with ESAs are comparable. The pivotal phase III trials[17,18] demonstrate comparable efficacy and dosing requirements for epoetin alfa and epoetin zeta
Perspective	Considers direct medical costs only, from perspective of NHS Wales	Yes
Time Horizon	Weekly costs considered	Yes, if accept CMA approach
Discount rate	Not applicable due to short time horizon of analysis	N/A
Efficacy	ESA efficacy assumed equivalent	Yes, was approach adopted by NICE in 2006 clinical guideline
Adverse effects	Not considered in analysis. All outcomes assumed to be comparable	Yes, if accept CMA approach
Utility values	N/A	N/A
Resource use		
Unit costs	Based mainly on BNF	Yes
Model Provided?	No	Not necessary to see this model

Table 2B. Results of additional cost minimisation analysis, using a standardised epoetin dose[2]

Drug	Weekly dose (IU)	Weekly cost of admin (£)	Total cost per week (£)
Epoetin zeta	4,000−6,000	8.01-16.02	30.91-50.50
Epoetin alfa	4,000−6,000	8.01-16.02	30.58-50.01
Epoetin beta	4,000−6,000	8.01-16.02	38.25-61.51
Darbepoetin alfa	4,000−6,000	4.005-8.01	35.59-55.46