Scottish Medicines Consortium

epoetin zeta, 1000 IU/0.3ml, 2000 IU/0.6ml, 3000 IU/0.9ml, 4000 IU/0.4ml, 5000 IU/0.5ml, 6000 IU/0.6ml, 8000 IU/0.8ml, 10,000 IU/1.0ml, 20,000 IU/0.5ml, 30,000 IU/0.75ml and 40,000 IU/1ml solution for injection in pre-filled syringe (Retacrit®) No. (467/08)
Hospira UK Limited

09 May 2008

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

epoetin zeta (Retacrit®) is accepted for use within NHS Scotland for treatment of anaemia associated with chronic renal failure in adult and paediatric patients on haemodialysis and adult patients on peritoneal dialysis and for treatment of severe anaemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing dialysis.

Clinical studies in adult haemodialysis patients have demonstrated equivalence in correcting and maintaining haemoglobin levels when compared to another erythropoiesis stimulating agent (ESA). Unlike other ESAs, epoetin zeta is only licensed for administration by the intravenous route.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of anaemia associated with chronic renal failure in adult and paediatric patients on haemodialysis and adult patients on peritoneal dialysis and treatment of severe anaemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing dialysis.

Dosing information

Patients on haemodialysis, adult patients on peritoneal dialysis and adult patients with renal insufficiency not yet undergoing dialysis:
The starting dose is 50 IU/kg three times weekly intravenously. Dose adjustments should be made at a minimum of 4 weekly intervals. Target haemoglobin levels: between 10 and 12 g/dl in adult patients and between 9.5 and 11g/dl in paediatric patients.

Product availability date

28 April 2008

Summary of evidence on comparative efficacy

Epoetin zeta is a recombinant human erythropoietin (rhEPO) which stimulates red blood cell production by promoting survival, proliferation and differentiation of erythroid progenitors in the bone marrow. It is a biosimilar product to the reference drug epoetin alfa.

Efficacy in achieving correction of haemoglobin (Hb) has been assessed in 2 phase III trials; one correction phase study and one maintenance phase study comparing the efficacy and safety of intravenously (IV) administered epoetin zeta compared with epoetin alfa in patients with renal anaemia. Patients from both trials could continue treatment with epoetin zeta for a further 28 weeks in an open, follow-up safety trial.

The correction study was a double-blind (double–dummy), multicentre trial in 609 adult haemodialysis patients with end-stage renal failure. Patient baseline haemoglobin concentration was required to be below 9g/dL despite optimal iron supplementation with or without pre-treatment with epoetin during an open run-in anaemia work-up period of up to six weeks. Eligible patients were randomised equally to epoetin zeta or epoetin alfa three times a week for 24 weeks. Epoetin-naïve patients initially received 50 IU/kg per dose and patients who had previously received epoetin received a starting dose that was 75 IU/kg/week higher than their pre-trial dose. The maximum permitted dose was 200 IU/kg. Dose adjustments were permitted as required at 4-week intervals to achieve a stable target haemoglobin concentration of 11.0-12.0 g/dl.

The primary endpoints were the mean weekly dosage of epoetin per kg body weight and the mean haemoglobin levels during the last 4 weeks of treatment in the per protocol population. Equivalence of epoetin zeta and epoetin alfa was analysed by calculating the 95% Confidence Intervals (CI) for the mean (test-reference) difference with predefined equivalence margins for dosage (initially ±15 IU/kg/week, later revised with EMEA approval to ±45 IU/kg/week) and for haemoglobin (±1g/dl).

The mean (SD) weekly dose over the last four weeks of treatment for epoetin zeta was 182.20 (118.11) IU/kg, compared with 166.14 (109.85) IU/kg/week for epoetin alfa; a mean difference of 16 IU/kg/week (corresponding to 9.6% of reference dose) and 95% CI (-3.21 to 35.34 IU/kg/week) were outside the initial pre-specified equivalence range but within the

revised equivalence range. The mean (SD) haemoglobin concentration over the last four weeks of treatment for epoetin zeta was 11.61 (1.27) g/dl, compared with 11.63 (1.37) g/dl for epoetin alfa (95% CI for the difference: -0.25 to 0.20 g/dl) and within the predefined equivalence range.

The maintenance study was a double-blind, crossover, multiple-dose, multicentre trial in 313 adult patients with chronic kidney disease (CKD) stage 5 and renal anaemia currently on epoetin treatment and on stable adequate dialysis, both for at least three months. Patients entered a 12-16 week (maximum 18 weeks) open run-in phase and were required to reach a target haemoglobin range of 10.5-12.5g/dl with constant epoetin alfa dosage and no intra-individual change in haemoglobin that exceeded 0.6g/dl over four weeks. Eligible patients were randomised equally to either epoetin alfa or epoetin zeta at the dose received during the last 4 weeks of the run-in phase. Dose adjustments were permitted every 4 weeks after evaluation of haemoglobin levels and only recommended in patients with optimal iron status. After 12 weeks, patients were switched over to the alternative medication, without changing dose, for a further 12 weeks.

The primary efficacy endpoint was the intra-individual change (epoetin zeta-epoetin alfa) in mean weekly dosage per kg body weight of each product during the double-blind treatment period and in mean haemoglobin level during double-blind treatment with each study drug in the per protocol population. The equivalence margin for dosage was ±45 IU/kg/week and for haemoglobin was ±0.6 g/dl.

The mean (range) weekly dosage over the double-blind period was 92.68 (12.74-398.41) IU/kg/week for patients receiving epoetin zeta and 92.58 (10.53–393.07) IU/kg/week for patients receiving epoetin alfa (95% CI for the difference: -4.67 to 4.29 IU/kg/week) and within the predefined equivalence range. Minor dose adjustments were required to maintain steady haemoglobin levels when switching between treatments due to variations in bioactivity. The mean (range) Hb level over the double-blind phase for epoetin zeta was 11.35 (8.96-14.22) g/dl compared with 11.54 (8.74-13.84) g/dl for epoetin alfa (95% CI for the difference: 0.09 to 0.28 g/dl) and within the predefined equivalence range.

Summary of evidence on comparative safety

Epoetin zeta administered intravenously showed a similar safety profile to epoetin alfa. In both studies, infections, infestations and vascular disorders were the most commonly reported.

Apart from 11 patients in the correction study and 3 patients in the maintenance study who had tested positive at baseline, no patients developed non-neutralising anti-erythropoietin antibodies and there were no cases of pure red cell aplasia (PRCA) during either study.

Summary of clinical effectiveness issues

The sponsor has presented two trials in adult haemodialysis patients with only intravenous dosing. No information has been supplied for paediatrics, peritoneal dialysis patients or patients not yet receiving dialysis. Although biosimilar to epoetin alfa, epoetin zeta is not licensed for subcutaneous use because the immunogenicity data in patients at risk for antibody-induced PRCA are not sufficient.

European Pharmacopoeia release specifications for epoetin allow the content of the final product to be within 80-125% of the nominal (labelled) content. There were between-

treatment differences of about 10% in the nominal doses required to correct and maintain target haemoglobin in the trials. In addition, there were differences in bioactivity and assay methods which could account for the observed differences, however the differences in bioactivity were within tolerated limits. The EPAR for epoetin zeta concluded that comparable clinical efficacy had been demonstrated not only with regard to haemoglobin but also with regard to epoetin dose.

Since pre-marketing data are limited the sponsor has provided the EMEA with an acceptable Risk Management Plan (RMP) in order to further study the safety profile with particular regard to PRCA and thrombotic vascular events. The RMP is also to include monitoring for other CNS events in addition to hypertensive encephalopathy and a proposal on how to monitor blood pressure in both naive and pre-treated patients in the post -marketing phase. The sponsor has also committed to perform a subcutaneous study with the same reference product.

The European Medicines Agency (EMEA) has recently reviewed the safety of epoetins in response to suggested increase in the risk of mortality and cardiovascular morbidity where treatment with epoetins had targeted high haemoglobin levels. They have concluded that the benefits of epoetins continue to outweigh their risks in the approved indications but suggested changes to product information: epoetins should be used in the treatment of anaemia only if associated with symptoms; the target haemoglobin range for all epoetins should be 10-12 g/dl with a warning not to exceed a concentration of 12 g/dl, and there should be strict adherence to SPCs regarding indications and dosing recommendations.

Although clinical equivalence has been shown for epoetin zeta compared with epoetin alfa for the surrogate endpoints of correction and maintenance of Hb concentration, no direct health outcomes were measured such as mortality and quality of life studies.

Summary of comparative health economic evidence

The manufacturer presented a cost-minimisation analysis comparing epoetin zeta to three other erythropoiesis stimulating agents (ESAs) used in patients with chronic kidney disease. The manufacturer did not present any economic analysis for paediatric patients.

On the basis of recent guidelines, the manufacturer assumed that the ESAs can be considered to have comparable efficacy. The analysis looked at costs per week in the induction and maintenance phases using the dosing given in the SPCs of the respective products and also using an approach of ESAs being given in a standard weekly dose based on international units. The costs of drug administration were included. The results suggested that epoetin zeta would be preferred on cost-minimisation grounds in many cases and as such the economics case was considered to be demonstrated. Though the case was not formally demonstrated for all patients covered by the licensed indication, the acceptance of equivalent efficacy at similar or lower cost would apply equally to all patients.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

UK Renal Association; Clinical Practice Guideline, 4th edition, 2007.

National Institute for Health and Clinical Excellence (NICE) clinical guideline 39 on anaemia management in people with chronic kidney disease (2006). Covers diagnostic evaluation, assessment and management of anaemia in patients with CKD and assessment and optimisation of erythropoiesis and monitoring treatment of anaemia. States that there is no evidence to distinguish between ESAs in term of efficacy.

National Collaborating Centre for Chronic Conditions, Royal College of Physicians. Guideline of Anaemia management in chronic kidney disease (2006). The guideline covers the same topics as NICE but is more detailed.

Joint Specialty 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).

A Scottish Intercollegiate Guideline Network (SIGN) guideline on chronic kidney disease is planned for publication in Spring 2008. Although there is no specific focus on anaemia associated with chronic kidney disease a small section will include ESAs in management of anaemia. SIGN February 2008.

Additional information: previous SMC advice

After review of a full submission, the Scottish Medicines Consortium (SMC) issued advice on 12 November 2007 that epoetin delta (Dynepo®) is accepted for use within NHS Scotland for the treatment of anaemia in patients with chronic renal failure. It may be used in patients on dialysis and in patients not on dialysis. Clinical studies have demonstrated epoetin delta's efficacy and safety profile in correcting and maintaining haemoglobin levels for up to a year in predialysis, haemodialysis and peritoneal dialysis patients, when administered via both the subcutaneous and intravenous routes.

After review of a full submission, the Scottish Medicines Consortium (SMC) issued advice on 7 April 2008 that methoxy polyethylene glycol-epoetin beta (Mircera®) is accepted for use within NHS Scotland for the treatment of anaemia in patients with chronic renal failure. Clinical studies have demonstrated the efficacy of methoxy polyethylene glycol-epoetin beta in correcting and maintaining haemoglobin levels for up to a year in dialysis patients, when administered by either the subcutaneous or intravenous route. Non-inferiority to other erythropoiesis stimulating agents, with respect to achieving and maintaining haemoglobin levels, was demonstrated.

Additional information: comparators

Five ESAs are available for the management of renal anaemia, epoetin alfa, epoetin beta, darbepoetin alfa, epoetin delta and methoxy polyethylene glycol-epoetin beta.

Cost of relevant comparators

Drug	Dose regimen	Total dose	Cost per month (£)
epoetin zeta	**Hb Correction – Haemodialyis and patients not yet receiving dialysis; 50 IU/kg three times a week (IV)** **Hb Maintenance – Haemodialysis; 75-300 IU/kg weekly (IV).**	**10,500 IU weekly** **5,250-21,000 IU weekly**	**272** **204 to 543**
epoetin beta	**Hb Correction –** 40 IU/kg (IV) three times per week or 20 IU/kg (SC) three times per week to a maximum of 720 IU/kg weekly (IV or SC) **Hb Maintenance –** No specific dose in SPC	8,400 IU weekly (IV) or 4,200 IU weekly (SC) to a maximum of 50,400 IU weekly (IV or SC)	281 (IV) or 140 (SC) to a maximum of 1,590 (IV or SC)
methoxy polyethylene glycol-epoetin beta	**Hb Correction –** ESA - naïve patients -0.6 micrograms/kg fortnightly (IV or SC) **Hb Maintenance –** dose equal to twice the previous fortnightly dose 120–360 micrograms monthly (IV or SC)	42micrograms fortnightly (IV or SC) 120-360micrograms monthly (IV or SC)	156 (IV or SC) 234 to 584 (IV or SC)
epoetin alfa	**Hb Correction –** 50 IU/kg three times a week (IV or SC) **Hb Maintenance –** 75-300 IU/kg weekly (IV or SC)	10,500 IU weekly 5,250-21,000 IU weekly	302 (IV or SC) 151 to 528 (IV or SC)
epoetin delta	**Hb Correction –** 50 IU/kg (IV) three times a week or 50 IU/kg (SC) twice weekly **Hb Maintenance –** No specific dose in SPC	10,500 IU weekly (IV) or 7,000 IU weekly (SC)	272 (IV) or 181 (SC)
darbepoetin alfa	**Hb Correction –** 0.45 micrograms/kg weekly (IV or SC) or in non-dialysis patients 0.75 micrograms/kg fortnightly (SC) **Hb Maintenance –** Correction dose continued weekly, fortnightly (IV or SC) and in stable non dialysis patients monthly (SC)	31.5micrograms weekly (IV or SC) 52.5micrograms fortnightly (SC)	187 (IV or SC) 156 (SC)

Abbreviations: kg (kilogram), IU (international unit), IV (intravenous), SC (subcutaneous) and ESA (erythropoietin stimulating agent). Doses are for general comparison and do not imply therapeutic equivalence. Costs for epoetin zeta are from Hospira UK Limited. Costs for other ESAs are from

eVadis on 28th February 2008. Costs calculated for a 70kg patient on haemodialysis unless otherwise stated. Doses are rounded to the nearest practical syringe size and assume one dose per pre-filled syringe. Costs for correction doses are for the initial dose and may be subject to change until the target haemoglobin level is obtained.

Additional information: budget impact

The manufacturer estimated the total value of prescribing in the ESA market following the introduction of epoetin zeta. The manufacturer assumed that the four ESAs used in the economic evaluation would have an equal market share. On the basis of maximum ESA dosing and including drug administration costs, the manufacturer estimated that the total cost of ESAs would be £17.9m in year one rising to £18.2m in year five. Using minimum ESA doses, the costs were estimated at £5.3m and £5.4m in years one and five respectively. Total patient numbers were 2058 in year one and 2100 in year five. No net budget impact figures were presented and the figures do not take in to account national contract prices for comparator products.

Advice context:

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

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 22 April 2008.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

European Medicines Agency (EMEA), European Public Assessment Report (EPAR) for epoetin zeta. http://www.emea.europa.eu/humandocs/Humans/EPAR/retacrit/retacrit.htm

EMEA. Public Statement. Epoetins and the risk of tumour growth progression and thromboembolic events in cancer patients and cardiovascular risks in patients with chronic kidney disease. http://www.emea.euopa.eu/pdfs/human/pres/pus/49618807en.pdf

Stada R&D GmbH. Final Study Report. CT-830-04-0003. Evaluation of the therapeutic equivalence of two different formulations containing epoetin (Epoetin Stada (epoetin zeta) vs. Erypo® (epoetin alfa)) administered intravenously in the correction phase of renal anaemia.

Wizemann V, Rutkowski B, Baldamus C, Scigalla P, Group RK. Comparison of the therapeutic effects of epoetin zeta to epoetin alfa in the maintenance phase of renal anaemia treatment. Curr Med Res Opin 2008.