Scottish Medicines Consortium



epoetin theta, 1,000 IU/0.5mL, 2,000 IU/0.5mL, 3,000 IU/0.5mL, 4,000 IU/0.5mL, 5,000 IU/0.5mL, 10,000 IU/1mL, 20,000 IU/1mL, 30,000 IU/1mL solution for injection in pre filled syringe (Eporatio[®]) No.(620/10) Ratiopharm UK Limited

04 June 2010

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 theta (Eporatio[®]) is accepted for use within NHS Scotland.

Licensed indication under review: the treatment of symptomatic anaemia associated with chronic renal failure in adult patients.

Epoetin theta demonstrated non-inferiority to another erythropoietin analogue in maintaining stable haemoglobin levels in renal failure associated anaemia both in patients not yet receiving dialysis (subcutaneous route) and in those receiving haemodialysis (intravenous route).

The British National Formulary advises that it is good practice to prescribe biological medicinal products by brand name.

Other erythropoietin stimulating agents are available at lower cost.

Overleaf is the detailed advice on this product.

Chairman, Scottish Medicines Consortium

Indication

Treatment of symptomatic anaemia associated with chronic renal failure in adult patients.

Dosing information

The dose and frequency of administration should be individualised according to the patient's clinical course and condition, and titrated to achieve a target haemoglobin range (10 to 12g/dL). The maximum dose should not exceed 700 IU/kg per week.

In symptomatic anaemia associated with chronic renal failure epoetin theta can be administered either subcutaneously, (preferable in patients not undergoing haemodialysis), or intravenously.

See Summary of Product Characteristics (SPC) for dose details.

Treatment with epoetin theta should be initiated under the supervision of physicians experienced in the management of patients with chronic renal failure.

Product availability date

01 December 2009

Summary of evidence on comparative efficacy

Epoetin theta (Eporatio[®]) is a recombinant human erythropoietin that stimulates red blood cell production by promoting survival, proliferation and differentiation of erythroid progenitors in the bone marrow.

Evidence to support efficacy for this indication is from four active-controlled studies in patients with chronic renal failure (CRF) -associated anaemia.

Two randomised, controlled, blinded phase II haemoglobin (Hb) correction studies examined the dose-dependent efficacy of epoetin theta in anaemic patients with CRF. The first study recruited patients not yet treated with dialysis, who had a glomerular filtration rate (GFR) <60 mL/min/1.73m², while the second recruited patients who had been receiving haemodialysis two or three times a week for at least 12 weeks. In both studies patients were ≥21 years, had a stable Hb ≤10.0g/dl and had not received an epoetin in the previous 12 weeks, or a long-acting epoetin in the previous 6 months. After a screening phase, patients entered a four week fixed-dose phase and were randomised equally to treatment groups, stratified by country. In the first study, patients received three times weekly subcutaneous treatment with 20, 30, 40, 80 and 120 IU/kg epoetin theta, or 20 IU/kg epoetin beta; in the second, patients received three times weekly intravenous treatment with 40, 60, 80, 120 IU/kg epoetin theta, or 40 IU/kg epoetin beta. This was followed by an adaptation phase, in which each patient's dose was adjusted until the target Hb response (11 to 12g/dL) was reached, or for a maximum of 20 weeks if target was not reached.

The primary outcome in both studies was the dose-dependent average weekly increase in Hb within the fixed-dose phase, in the intention-to-treat (ITT) population (all randomised patients), comprising 134 and 150 patients in the first and second study, respectively. Epoetin theta was to be regarded as effective if there was a statistically significant difference in the increase of Hb levels after treatment with 20 IU/kg (40 IU/kg in the second study)

compared with 120 IU/kg epoetin theta given three times weekly. Exploratory comparisons of the epoetin theta dose groups versus epoetin beta were also performed.

The primary outcome was achieved in both studies. During the fixed-dose phase, the mean (\pm SD) weekly increase of Hb in the epoetin theta 120 IU/kg group was significantly higher than in the 20 (40 in the second study) IU/kg group: 0.73 \pm 0.33 g/dL versus 0.20 \pm 0.28 g/dL and 0.58 \pm 0.27 g/dL versus 0.26 \pm 0.26 g/dL, respectively.

In both studies, numerically corresponding epoetin theta and beta groups produced identical Hb response rates (Hb level >11.0g/dL on two consecutive measurements in the adaption phase), similar mean times to Hb response and similar mean single doses three times in the week before response.

Two randomised, controlled, blinded, phase III non-inferiority studies compared the efficacy of epoetins theta and beta in maintaining Hb levels in patients with CRF-associated anaemia. The first study recruited patients not yet receiving dialysis (with a GFR <60mL/min/1.73m²) who were on maintenance treatment with subcutaneous epoetin beta, while the second recruited patients receiving haemodialysis for at least 6 months and maintenance treatment with intravenous epoetin beta. All patients were required to have stable Hb levels \geq 9.5g/dL and <12g/dL.

After a screening visit and a two week baseline period when patients continued taking their pre-study treatment, patients were randomised 2:1, stratified by country, to 24 weeks treatment with an equivalent dose and same administration route of epoetin theta or to remain on the same dose and administration route of epoetin beta. During this phase the epoetin dose could be adjusted to maintain Hb values within the target interval (I=[baseline-1.0, baseline+1.0] \cap [9.5, 12.0]). The evaluation period (EVP) was weeks 15 to 26. Patients were followed for up to 30 days after the last dose of study medication.

The primary endpoint was change of Hb level from baseline (mean of the 3 visits during the baseline period) to end of treatment (mean of EVP). The primary analysis was based on the according to protocol (ATP) population (all randomised patients treated with study medication with no major protocol violations), comprising 240 and 224 patients in the first and second study, respectively. A difference of 1.0g/dL between treatment groups was considered the greatest clinically acceptable difference and denoted the limit of non-inferiority.

In both studies mean Hb values were similar in both treatment groups at baseline and during the EVP for the ATP population. In the first study, from a mean (±SD) baseline of 10.88 \pm 0.59g/dL and 10.93 \pm 0.61g/dL for the epoetin theta and beta groups respectively, the change from baseline was 0.19 \pm 0.80g/dL and 0.15 \pm 0.73g/dL respectively, giving an estimated difference (\pm SE) of 0.01 \pm 0.11g/dL (95% confidence interval (CI): -0.20 to 0.22). In the second study, the corresponding figures were from a mean baseline of 10.86 \pm 0.62g/dL and 10.83 \pm 0.59g/dL, the change from baseline was -0.21 \pm 0.82g/dL and -0.17 \pm 0.96g/dL, giving an estimated difference of -0.01 \pm 0.11g/dL (95% CI: -0.24 to 0.21). Thus the primary endpoint was met in each study and epoetin theta was considered non-inferior to epoetin beta. It was found in both studies that baseline Hb values had an effect on the outcome of the primary endpoint: the higher the baseline value, the lower the mean change from baseline. The findings for the ITT populations, all randomised patients, supported the primary analysis of non-inferiority in the ATP populations. During the EVP, the mean weekly dose of epoetins theta and beta was similar in both studies.

Summary of evidence on comparative safety

Overall the safety profile of epoetin theta is consistent with the known safety profile of epoetins and as expected for the study populations. There were no new or unexpected findings. There were no clinically relevant differences in treatment emergent adverse events between the epoetin theta and beta groups across or within the studies. Approximately 9% of patients can be expected to experience an adverse event; most commonly hypertension, influenza-like illness and headache.

The European Medicines Agency (EMA) note that important risks associated with erythropoietin treatment in general are pure red cell aplasia, thrombotic vascular events and possible tumour growth promoting potential.

Summary of clinical effectiveness issues

The marketing authorisation application for epoetin theta was a complete and independent application, not an application for a 'similar biological medicinal product.'

Epoetin theta demonstrated non-inferiority to epoetin beta in maintaining stable Hb levels in chronic renal failure-associated anaemia both in patients not yet receiving dialysis (treatment by the subcutaneous route) and in those receiving haemodialysis (treatment by the intravenous route). It has not been compared with other erythropoiesis stimulating agents (ESAs).

Epoetin theta is licensed for use via the subcutaneous and intravenous routes in symptomatic anaemia associated with chronic renal failure whereas some erythropoietin analogues are only licensed for use via the intravenous route.

Epoetin theta can be administered once weekly for Hb maintenance, however other ESAs are available which require less frequent dose administration e.g. once every two weeks or once every month.

The shelf-life of epoetin theta (like Eprex[®]) is 18 months compared with 24 months for other ESAs.

No increased immunogenicity has been demonstrated in patients who switched from epoetin beta (NeoRecormon[®]) to epoetin theta.

Summary of comparative health economic evidence

The manufacturer presented a cost-effectiveness analysis comparing epoetin theta with epoetin beta for the treatment of symptomatic anaemia associated with chronic renal failure. This examined cost-effectiveness in four scenarios:

- Initiation of subcutaneous treatment in renal patients not on dialysis
- Initiation of intravenous treatment in renal patients already on dialysis
- Maintenance of subcutaneous treatment in renal patients not on dialysis already on an ESA
- Maintenance of intravenous treatment in renal patients already on dialysis and on an ESA.

The time horizon for the analysis was 16 weeks in the first two scenarios and one year in the remaining two scenarios.

Clinical data to support the assumption of comparable efficacy of epoetin theta and epoetin beta were based on four studies in patients with chronic renal failure corresponding to the four treatment scenarios outlined above. In the cost-effectiveness analysis the mean cost per patient brought to Hb target was estimated based on the different drug acquisition costs of epoetin theta and epoetin beta but also included non-significant differences in outcome measures from the clinical trials. This included the mean dose required to achieve target Hb, proportion achieving target Hb, blood transfusion rates and the proportion of withdrawals. Based on this the manufacturer estimated epoetin theta would be associated with cost savings of £53, £211, £61 and £526 per patient for each of the four scenarios respectively.

The following weaknesses were noted:

- The savings estimated in the base case analysis included savings based on nonsignificant differences between the treatments. When these differences were removed the manufacturer estimated the use of epoetin theta would result in savings of £106, £271, £161 and £497 per patient based on drug acquisition costs alone.
- No comparison was made with other ESAs available in Scotland. SMC experts indicate that other ESAs such as darbepoetin and epoetin alfa are also widely used and may be available at a lower cost than epoetin theta.

Overall, the analysis shows that epoetin theta would be associated with savings compared with epoetin beta based on drug costs alone. However no comparison has been made with other ESAs, some of which are available at lower cost and may require less frequent administration in the pre-dialysis setting.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

Epoetin theta is also licensed for an additional indication: treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

This indication is included in National Institute for Health and Clinical Excellence (NICE) multiple technology appraisal (MTA) 142, 'Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia' (May 2008), which states that erythropoietin analogues are not recommended for routine use in the management of cancer treatment-induced anaemia, except in the following circumstances:

- Erythropoietin analogues are recommended in combination with intravenous iron as an
 option for the management of cancer treatment-induced anaemia in women receiving
 platinum-based chemotherapy for ovarian cancer who have symptomatic anaemia with a
 haemoglobin level of 8g/100mL or lower. The use of erythropoietin analogues does not
 preclude the use of existing approaches to the management of anaemia, including blood
 transfusion where necessary.
- Erythropoietin analogues in combination with intravenous iron may be considered for people who cannot be given blood transfusions and who have profound cancer treatment-related anaemia that is likely to have an impact on survival.

NHS Quality Improvement Scotland has advised that this NICE MTA is valid in NHS Scotland. The use of epoetin theta for cancer treatment-induced anaemia has therefore not been reviewed by the SMC.

The Scottish Intercollegiate Guidelines Network issued clinical guideline number 103, 'Diagnosis and management of chronic kidney disease', in 2008. It states that ESAs should be considered in all patients with anaemia of chronic kidney disease to improve their quality of life. In patients with chronic kidney disease treated with ESAs, the haemoglobin should normally be kept between 10 and 12g/dL. The guideline notes there may be circumstances where the use of ESAs is inappropriate.

The NICE clinical guideline 39 on 'Anaemia management in people with chronic kidney disease' (2006), states that there is no evidence to distinguish between ESAs in term of efficacy. Key considerations for patients with anaemia associated with kidney disease are: ESAs are prescribed when clinically indicated; the ESA supply, route of supply and storage arrangements are clearly defined, secure and convenient; and the administration and monitoring of anaemia treatment is as efficient, comfortable and least disruptive as possible.

The UK Renal Association is currently updating its Clinical Practice Guidelines on 'Anaemia in chronic kidney disease'. A draft document published in February 2010 recommends that treatment with ESAs should be offered to patients with anaemia of chronic kidney disease who are likely to benefit in terms of quality of life and physical function, and to avoid transfusion in patients considered suitable for transplantation. They recommend that choice of ESA is based on local availability, target Hb is 10.5 to 12.5g/dL, and suggest that less frequent administration using long acting ESAs may be the treatment of choice in non-haemodialysis patients.

Additional information: comparators

Other epoetin analogues licensed for use in the UK are epoetin beta, epoetin alfa and epoetin zeta. Darbepoetin alfa is a hyperglycosylated derivative of epoetin and methoxy polyethylene glycol-epoetin beta is a continuous erythropoietin (EPO) receptor activator. Both these agents have a longer duration of action than epoetin analogues.

Cost of relevant comparators

Drug	Dose regimen* - maintenance treatment in chronic renal failure	Cost per year (£)
Epoetin theta	By intravenous injection 20 to 233 IU/kg three times a week By subcutaneous injection the weekly dose can be given once or in divided doses three times a week	1,869 to 15,890
Epoetin beta	By intravenous injection 20 to 240 IU/kg three times a week By subcutaneous injection the weekly dose can be given subcutaneously once a week or in divided doses three or seven times per week	2,188 to 18,601

Epoetin zeta	By intravenous injection 25 to 200 IU/kg three times a week	1,765 to 12,354
Epoetin alfa (Eprex [®] Janssen Cilag)	By intravenous or subcutaneous injection 25 to 200 IU/kg three times a week	1,726 to 12,079
Epoetin alfa (Binocrit [®] Sandoz)	By intravenous injection 25 to 200 IU/kg three times a week	1,588 to 11,118
Methoxy polyethylene glycol-epoetin beta	By intravenous or subcutaneous injection 120 to 360 micrograms once a month	2,290 to 6,8 71
Darbepoetin**	By intravenous injection 20 to 60 micrograms once a week. Once monthly dosing by subcutaneous injection is possible in some patients.	1,527 to 4,581

Doses are for general comparison and do <u>not</u> imply therapeutic equivalence. Costs from eVadis on 15.03.10. Costs based on 70kg body weight. *See relevant Summary of Product Characteristics (SPC) for dose details ** Dose range based on NICE Clinical Guideline 39 as not specified in SPC.

Additional information: budget impact

The manufacturer estimated that there would be savings of £558k over the next 5 years based on patients switching to epoetin theta from epoetin alfa and epoetin beta. No annual saving estimates were presented by the manufacturer. The manufacturer estimated that there would be 131 patients treated with epoetin theta in year 1 based on a market share of 5%, rising to 392 in year 5 based on a market share of 12%. It should be noted that the price of ESAs are subject to national contracting arrangements which may influence whether any savings can be achieved in clinical practice.

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 12 April 2010.

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

Clinical Study Synopsis. Efficacy and safety of subcutaneous administration of XM01 and Epoetin beta for treatment of anaemia in chronic renal failure patients not yet receiving dialysis (A multinational, multicentre, randomised, controlled, double-blind, parallel group Phase II study). BioGeneriX Study No: CSR XM01-04.

Clinical Study Synopsis. Efficacy and safety of intravenous administration of XM01 and Epoetin beta for treatment of anaemia in chronic renal failure patients receiving haemodialysis (a multinational, multicentre, randomised, controlled, double-blind, parallel-group Phase II study). BioGeneriX Study No: CSR XM01-05.

Clinical Study Synopsis. Efficacy and safety of subcutaneous administration of XM01 compared to epoetin beta in anaemic chronic renal failure patients not yet receiving dialysis and in maintenance phase treatment with epoetin beta (a multinational, multicentre, randomised, controlled, doubleblind, comparative, parallel group Phase III study). BioGeneriX Study No: CSR XM01-06.

Clinical Study Synopsis. Efficacy and safety of intravenous administration of XM01 compared to epoetin beta in anaemic chronic renal failure patients on haemodialysis and in maintenance phase treatment with epoetin beta (a multinational, multicentre, randomised, controlled, double-blind, comparative, parallel group Phase III study). BioGeneriX Study No: CSR XM01-07.

The European Medicines Agency (EMA) European Public Assessment Report. Epoetin theta (Eporatio[®]) 11/03/10. EMA H/C/001033. <u>www.ema.europa.eu</u>