epoetin alfa 1,000 IU/0.5mL, 2,000 IU/1mL, 3,000 IU/0.3mL, 4,000 IU/0.4mL, 5,000 IU/0.5mL, 6,000 IU/0.6mL, 7,000 IU/0.7mL, 8,000 IU/0.8mL, 9,000 IU/0.9mL, 10,000 IU/1mL, solution for injection in prefilled syringe (Binocrit®) No. (597/10)

Sandoz Ltd

15 January 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 alfa (Binocrit®) is accepted for use within NHS Scotland for:

Treatment of symptomatic anaemia associated with chronic renal failure in adult and paediatric patients:

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

Binocrit® can be used 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 (haemoglobin 10 to 13g/dL [6.2 to 8.1 mmol/L], no iron deficiency), if blood saving procedures are not available or insufficient when the scheduled major elective surgery requires a large volume of blood (4 or more units of blood for females or 5 or more for males).

Epoetin alfa (Binocrit®) is a biosimilar product and has demonstrated equivalency in terms of efficacy and safety to a reference product (epoetin alfa (Eprex®)).

Unlike some other erythropoiesis stimulating agents, Binocrit® is only licensed for administration by the intravenous route in the indications under review.

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

Overleaf is the detailed advice on this product.

Chairman, Scottish Medicines Consortium

Indication

Treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult and paediatric patients:

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

Binocrit® can be used 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 (haemoglobin (Hb) 10 to 13 g/dL [6.2 to 8.1 mmol/L], no iron deficiency), if blood saving procedures are not available or insufficient when the scheduled major elective surgery requires a large volume of blood (4 or more units of blood for females or 5 or more units for males).

Dosing information

In the treatment of symptomatic anaemia in adult and paediatric CRF patients, Binocrit® should be administered intravenously and titrated to achieve a target haemoglobin range 10 to 12 g/dL (adults) or 9.5 to 11g/dL (children).

In the treatment of adult surgery patients in an autologous predonation programme, Binocrit® should be administered intravenously.

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

Treatment with Binocrit® has to be initiated under the supervision of physicians experienced in the management of patients with the above indications.

Product availability date

11 March 2008

Summary of evidence on comparative efficacy

Epoetin alfa (Binocrit®) is an erythropoiesis stimulating agent (ESA). It is a biosimilar product to the reference drug epoetin alfa (Eprex®). In both products the active substance has a primary structure identical to endogenous human erythropoietin.

Evidence to support efficacy is from a study that evaluated a 1:1 dose conversion from Eprex® to Binocrit® based on Hb assessment in anaemic CRF patients on haemodialysis. The study consisted of two parts. Part I was designed as a double-blind, randomised, multicentre, equivalence study. The initial phase of part I involved dose adjustment and maintenance of Hb levels and lasted until week 24. The second phase was a four-week evaluation period during which the primary efficacy endpoint was determined. In Part II (week 29 to 56) all patients received open-label Binocrit® to determine its long-term safety profile.

The study recruited clinically stable adult haemodialysis patients (Hb 10 to 13g/dL ≥12 weeks) and stable intravenous (IV) dose of Eprex® ≥8 weeks before screening and a maximal weekly dose of 300 IU/kg body weight. Patients had to have received dialysis for ≥6 months (three times weekly) before study entry. Following a screening/baseline period of

up to 2 weeks, eligible patients were randomised 2:1 to switch to IV Binocrit® (n=314) or to continue to receive Eprex® (n=164) three times weekly initially maintaining the epoetin dose administered before randomisation. Dose adjustments were allowed every other week if required.

The primary endpoint was mean absolute change in Hb levels from the baseline period to the evaluation period for the per-protocol (PP) patient population, (all patients who completed the double-blind treatment period without any major protocol violations). In the primary PP population, mean change in Hb was 0.147 g/dL in the Binocrit® group and 0.063 g/dL in the Eprex® group. The treatment difference was 0.084 g/dL, 95% confidence interval (CI); -0.170 to 0.338. Therapeutic equivalence was confirmed as the CI was within the predefined range of ±0.5 g/dL.

The mean absolute change in Hb levels from baseline to the evaluation period for the intention-to-treat (ITT) population (all randomised patients who received at least one dose of the study medication and for whom at least one post-baseline value for the primary endpoint was available) was 0.003 g/dL in the Binocrit® group and -0.187 g/dL in the Eprex® group. The treatment difference was 0.189 g/dL, 95% CI; -0.03 to 0.418 which is within the predefined range of ±0.5 g/dL and therapeutic equivalence was confirmed.

There were also no significant differences between treatment groups in any other endpoint including range of weekly Hb values over the course of the study, proportion of patients with Hb values within the target range during the double-blind treatment period; response to treatment; proportion of patients with changes in the epoetin dosage; frequency, number and type of transfusions; quality of life; and overall efficacy as judged by the investigator.

Summary of evidence on comparative safety

In the pivotal study the adverse event profile was consistent with this advanced dialysis patient population, and comparable between treatment groups. Vascular disorders and cardiac disorders were more frequently reported with Binocrit® than Eprex® (32% versus 27%) and (17% versus 14%), respectively.

In the double blind period, 258 treatment-emergent serious adverse events (SAEs) were documented in 112 patients (36%) of the Binocrit® group, and 99 SAEs in 56 patients (34%) of the Eprex® group. The death rate was consistent with the severe medical condition of these patients and only one death was assessed as related to the study drug. No increased immunogenicity was observed in patients receiving Binocrit® compared with Eprex®.

In the 26-week open label part II of the study, there were 1,736 treatment emergent adverse events (AEs) in 223 patients (90%) of the Binocrit® group and 926 in 127 patients (93%) of the Eprex®/Binocrit® group. Most AEs were of mild or moderate intensity, transient and resolved completely by the end of the study. In part II, there were 187 SAEs in 87 patients (35%) of the Binocrit® group, and 93 SAEs in 49 patients (36%) of the Eprex®/Binocrit® group. All SAEs were assessed as unrelated to study medication.

Overall, the adverse event profile for Binocrit® was comparable to that of Eprex®.

Summary of clinical effectiveness issues

Therapeutic equivalence of Binocrit® to Eprex® for IV administration was demonstrated in the pivotal study in anaemic CRF patients on haemodialysis. The EMEA has extrapolated equivalence to other indications. Binocrit® is only licensed for the intravenous route of administration in the indications under review.

Under guidance issued by the EMEA, regulatory dossiers for biosimilar products should provide data from at least two, adequately powered, randomised controlled studies to demonstrate bioequivalence. However, the EMEA acknowledged that at the time when Binocrit® was in clinical development, the reference product Eprex® could not be used as a comparator for subcutaneous administration, and the requirement for a second randomised study to document this route of administration was therefore waived. Due to the lack of evidence, the subcutaneous route is currently not recommended in renal patients with anaemia.

The clinical development programme for Binocrit® employed an Hb range of 10 to 13 g/dL as the target for the primary efficacy endpoint. The Medicines and Healthcare Products Regulatory Agency (MHRA) recommends a target range of 10 to 12g/dL and close monitoring of patients to ensure that the lowest approved dose of epoetin alfa is used to provide adequate control of anaemia and its symptoms. Overcorrection of haemoglobin concentration in patients with chronic kidney disease may increase the risk of death and serious cardiovascular events. Treatment with epoetins should be appropriately adjusted when symptoms of anaemia have been adequately brought under control, irrespective of haemoglobin concentration

There are other ESAs available which require less frequent dose administration e.g. once every two weeks or once every month compared with three times a week for Binocrit®.

Binocrit® syringes have been shown to be chemically and microbiologically stable for 24 months when stored at the recommended temperature of 2 to 8 ℃, compared with 18 months for Eprex® syringes (but 24 months for the other comparators).

No increased immunogenicity has been observed in patients who switched from Eprex® to Binocrit®.

Summary of comparative health economic evidence

The manufacturer presented a cost-minimisation analysis comparing epoetin alfa (Binocrit®) with epoetin alfa (Eprex®), darbepoetin alfa (Aranesp®), epoetin beta (NeoRecormon®) and epoetin zeta (Retacrit®), across all indications as covered by the licence. Two of the indications covered by the licence have previously been assessed for use in NHS Scotland. As such, only the CRF and autologous predonation indications were considered for review by SMC.

The assumption of equivalent efficacy between Binocrit® and Eprex® (the reference product) was supported by a study of patients with CRF undergoing haemodialysis. Clinical equivalence of Binocrit® compared with the other comparators was based on the NICE guideline for anaemia management in chronic kidney disease which states there is no evidence to distinguish between ESAs in terms of efficacy.

Only drug acquisition and administration costs were included in the analysis. It was assumed that there would be no difference between the treatments in terms of blood transfusion requirements or treatment of adverse events. As such, these costs were excluded from the analysis. This seems appropriate given the assumptions of equivalent efficacy and safety. Drug acquisition and administration costs were calculated according to the different indications based on the mean patient weight across the phase III studies. A time horizon of one year was assumed for the CRF indication and 4 weeks for the autologous predonation indication. Based on these treatment durations, the manufacturer estimated that Binocrit® would be associated with savings of £197 to £225 compared with Eprex®, £91 compared with darbepoetin alfa, £750 to £857 compared with epoetin beta and £178 compared with epoetin zeta.

Some weaknesses of the analysis were noted:

- Clinical evidence of equivalence to the reference product was only based on a study of patients with CRF.
- No clinical data were presented to support assumption of equivalent efficacy of Binocrit® with the other non-reference products. A class effect has been assumed.
- The estimated savings are based on the assumption that Binocrit® and the comparator drugs are both administered intravenously. In the indications under review Binocrit® is only licensed to be administered intravenously, whereas some of the comparators can be administered subcutaneously in CRF.

Overall, Binocrit® has a lower drug acquisition cost than the comparators and is likely to be cost-saving assuming IV administration. The assumption of equivalent efficacy between treatments was accepted together with a view that efficacy results based on a study of patients with CRF can be generalised to the autologous predonation indication, therefore the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

Binocrit® is licensed for two additional indications that have already been assessed for use in NHS Scotland:

- 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).

This indication is included in National Institute for Health and Clinical Excellence (NICE) multiple technology appraisal 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 for 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/100 ml 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.

- Binocrit can be used to reduce exposure to allogeneic blood transfusions in adult non-iron deficient patients prior to major elective orthopaedic surgery, having a high perceived risk for transfusion complications. Use should be restricted to patients with moderate anaemia (e.g. Hb 10 - 13 g/dl) who do not have an autologous predonation programme available and with an expected blood loss of 900 to 1800 ml.

This indication is included in NHS Quality Improvement Scotland (NHS QIS) Health Technology Assessment (HTA) 8 'The use of epoetin alfa before orthopaedic surgery in patients with mild anaemia' (2006) which concluded that epoetin alfa is not recommended for general use by NHS Scotland to reduce exposure to allogeneic blood transfusion in patients with mild anaemia prior to major elective orthopaedic surgery. Epoetin alfa is recommended for restricted use within NHS Scotland. It is a possible treatment option for patients with mild anaemia prior to major elective orthopaedic surgery who cannot receive blood transfusion, either due to their religious convictions or because suitable blood is unlikely to be available.

The Scottish Intercollegiate Guidelines Network issued clinical guideline number 103; the management of anaemia in patients with chronic renal failure, in 2008. It states that ESAs should be considered in all chronic kidney disease patients 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.

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 Clinical Practice Guidelines Fourth Edition (2007) recommends that treatment with ESAs should be offered to patients with anaemia of chronic kidney disease and haemoglobin consistently below 11g/dL who are likely to benefit in terms of quality of life and physical function, and to avoid transfusion in patients considered suitable for transplantation.

Additional information: comparators

The reference product is epoetin alfa (Eprex®). Other epoetin analogues licensed for use in the UK are epoetin beta (NeoRecormon®) and epoetin zeta (Retacrit®). Darbepoetin alfa (Aranesp®) is a hyperglycosylated derivative of epoetin and methoxy polyethylene glycol-epoetin beta (Mircera®) 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[#]	Cost per year (£)
Epoetin alfa (Binocrit® Sandoz**)**	**Intravenously 1,750 to 7,000 IU three times a week**	**1,588 to 5,559**
Epoetin alfa (Eprex® Janssen Cilag)	Intravenously 1,750 to 7,000 IU three times a week	1,784 to 6,246
Epoetin beta	Intravenously 5,600 to 16,800 IU three times a week	7,010 to 23,368
Epoetin zeta	Intravenously 1,750 to 7,000 IU three times a week	1,765 to 6,177
Darbepoetin	Intravenously or subcutaneously 20 to 60 micrograms per week*	1,558 to 4,673
Methoxy polyethylene glycol-epoetin beta	Intravenously or subcutaneously 120 to 360 micrograms once a month	2,434 to 7,301

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 30.10.09. Costs are based on body weight of 70kg. [#] Dose regimen based on maintenance treatment in adults receiving haemodialysis; regimens for other indications may vary. *Dose range based on Aranesp SPC and NICE Clinical Guideline 63.

Additional information: budget impact

The manufacturer estimated Binocrit® would be associated with savings of £10k in year 1 rising to £33k in year 5 within the CRF and autologous predonation indications. It was estimated that 94 CRF patients would be treated with Binocrit® in year 1 based on a market share of 4%, rising to 328 patients in year 5 based on a market share of 14%.

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.

Biosimilar medicines. A biosimilar medicine is a medicine which is similar to a biological medicine that has already been authorised (the 'biological reference medicine'). The active substance of a biosimilar medicine similar to the one of the biological reference medicine. Biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional.

This assessment is based on data submitted by the applicant company up to and including ***09 November 2009.***

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.

Sandoz Ltd. Data on file: Integrated Clinical Study Report (Part I and Part II) 2003-29-INJ-9/HX01, 2006.

Sandoz Ltd. Data on file: Integrated Clinical Study Report (Part I) 2003-29-INJ-9/HX01, 2007.

European Medicines Agency (EMEA). European Public Assessment Report: Epoetin alfa (Binocrit) 28/8/07 H-C-725 www.emea.europa.eu