Anaemia (cancer-treatment induced) - erythropoiesis-stimulating agents (epoetin and darbepoetin) (rev TA142)

Binocrit (epoetin alfa) from Sandoz: executive summary

Binocrit is a biosimilar of Eprex (Janssen-Cilag), in terms of quality, safety and efficacy. Binocrit was the first biosimilar recombinant human erythropoietin alfa agent approved by the EMA in 2007. Manufacturing biopharmaceuticals, which are complex recombinant proteins, requires high quality development and production processes. The EMEA has developed clear guidelines and a strict regulatory process for the approval of new versions of biopharmaceuticals to ensure the quality of approved products. Such medicines are assessed by the same standards as other biopharmaceuticals, regardless of the route of approval. Sandoz manufactures Binocrit in Europe at production facilities (including Rentschler Biotechnologie GmbH) with a long history in the manufacture of biopharmaceuticals. Manufacturing of biologics in Europe follow Good Manufacturing Practice; there is no difference in GMP standards for biosimilars and originator biologics. Biosimilars can be considered therapeutic alternatives to the reference product. (Weise et al 2012). Current clinical guidelines do not differentiate between different ESAs in relation to effectiveness and safety (Level I evidence) [Schrijvers et al. *Ann Oncol* 2010].

Biosimilars encourage innovation

Biosimilars, an innovation themselves, stimulate further innovation through competition. Benefitting from state-of-the-art analytics and improvements in manufacturing technology, biosimilars offer health systems high quality, affordable biopharmaceuticals. The introduction of biosimilars has enabled more patients to access high cost treatment, enabling "step changes" in treatment algorithms. The introduction of biosimilar filgrastim has enabled more patients to receive primary prophylaxis [Verpoort, Mohler, *Ther Adv Med Oncol*, 2009; Gascon P et al *Supportive Care in Cancer* 2013], which may in turn prevent more febrile neutropenia and improve cancer outcomes. Likewise in cancer-treatment induced anaemia, the uptake of biosimilar erythropoietin may allow more patients to access treatment with an ESA agent at Hb levels recommended in current international guidelines, preventing unnecessary infusions of blood, which is an expensive, scarce resource which carries an inherent risk of transfusion-transmitted diseases

Binocrit development program

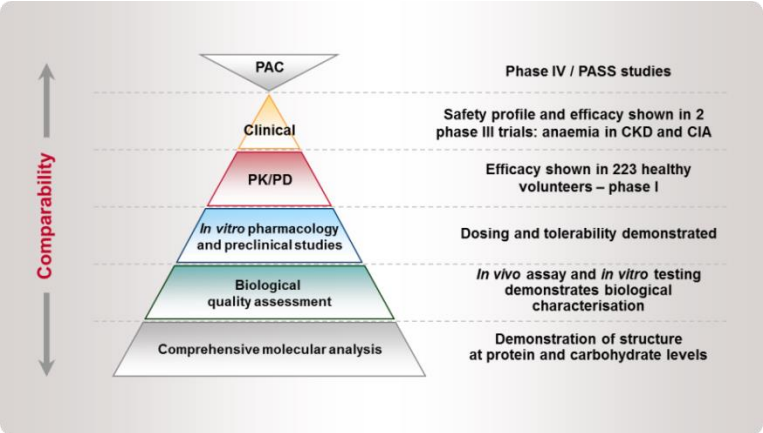

Table 1 Overview of phase I studies of Binocrit®

Study	Design	Study population	Dose and regimen	Duration
INJ-5 Sorgel et al, *BMC Clin Pharmacol,* 2009	Open, randomised (1:1), parallel-group	Healthy volunteers (n=80)	Multiple i.v. doses Binocrit® and comparator epoetin alfa 100 IU/kg body weight, three times weekly	4 weeks
INJ-12 Sorgel et al, *Pharmacology,* 2009	Open, randomised (1:1), parallel-group	Healthy volunteers (n=80)	Multiple s.c. doses Binocrit® and comparator epoetin alfa 100 IU/kg body weight, three times weekly	4 weeks
INJ-6 Sorgel et al, *Int J Clin Pharmacol Ther,* 2009	Open, randomised, parallel-group	Healthy volunteers (n=80)	Multiple s.c. doses Binocrit® and epoetin beta 100 IU/kg body weight, three times weekly	4 weeks

Table 2 Study INJ-11 overview (Weigang-Kohler et al, *Onkologie*, 2009)

Subjects	Adult patients with a confirmed diagnosis of a solid tumour who had received cyclic palliative, but not curative, chemotherapy with a cycle duration of 1–4 weeks (for at least 12 weeks) during the study. Patients were required to have: • chemotherapy-associated anaemia (Hb ≤10 g/dL at screening) • Eastern Co-operative Oncology Group (ECOG) performance status of 0, 1 or 2 • Life expectancy of ≥6 months.
Design	Double-blind, randomised, multi-centre, clinical phase III study. Screening/baseline period (week 0) and evaluation period (week 5–12).
Investigational medicinal product	Binocrit® solution for s.c. injection in pre-filled syringes containing 1000, 2000, 4000, 8000 and 10,000 IU epoetin, to be administered three times weekly.
Reference product	Erypo®/Eprex® FS, Janssen-Cilag, solution for s.c. injection in pre-filled syringes containing 1000, 2000, 4000, 8000 and 10,000 IU epoetin, to be administered three times weekly.
Study duration	12 weeks
Number of subjects	114 (74 Binocrit®, 40 epoetin alfa; safety population) 94 (60 Binocrit®, 34 epoetin alfa; ITT population) 64 (43 Binocrit®, 21 epoetin alfa; PP population)
Primary endpoint	Absolute increase in Hb value of ≥2.0 g/dL between the screening/baseline period and the evaluation period in the absence of RBC transfusion during the preceding four weeks.
Safety assessments	Adverse events, vital signs (blood pressure, heart rate), local tolerability, incidence of patients requiring change of antihypertensive therapy, presence of anti-epoetin antibodies.
Key findings	• Binocrit® is efficacious in the treatment of chemotherapy-induced anaemia, with comparable dose response to the reference product, Eprex®. • Treatment with Binocrit® increased Hb levels and improved patients' QoL. • Binocrit® demonstrated a similar safety profile to that of Eprex® in the treatment of patients with chemotherapy-induced anaemia.

Table 3 Study INJ-9 overview [Haag-Weber et al, *Clin Nephrol*, 2009] *(included for totality of data)*

Subjects	Clinically stable adults receiving haemodialysis t.i.w. for ≥6 months: • with Hb 10–13 g/dL for ≥12 weeks before screening • receiving comparator epoetin alfa, t.i.w., ≤300 IU/kg/week, for ≥8 weeks
Design	*Part I*: Double-blind, randomised, multi-centre, parallel-group equivalence phase III study to determine efficacy and safety (dose adjustment and maintenance of Hb level during weeks 1–24, evaluation at weeks 25–28). *Part II*: Open-label, multi-centre study focusing on long-term safety of Binocrit® (weeks 29–56).
Investigational medicinal product	Binocrit® solution for i.v. injection in pre-filled syringes containing 1000, 2000 or 4000 IU epoetin, to be administered t.i.w.
Reference product	Erypo®/Eprex® FS, Janssen-Cilag, solution for i.v. injection in pre-filled syringes containing 1000, 2000 or 4000 IU epoetin, to be administered t.i.w.
Key findings	• Binocrit® is therapeutically equivalent to Eprex® for the treatment of anaemia in patients with chronic renal failure on haemodialysis. • Binocrit® demonstrated a similar safety profile to that of Eprex®.

Post-approval studies

Table 3.1 Overview of post-approval studies of Binocrit® in CIA

Study	Study treatments	Patients	Key findings
Kerkhofs et al, *Future Oncol,* 2012	Binocrit® 30,000 or 40,000 IU/week (n=152)	Patients with various solid tumours in receipt of chemotherapy	• Hb response rate: 79% of evaluable patients • Similar response rate regardless of initial Binocrit® dose
Desrame et al, Poster presented at the ECC Amsterdam, 2013	Binocrit® (n=444)	Patients with various solid tumours (n=344) or haematological malignancies (n=100), in receipt of chemotherapy	• Significant increase in Hb from baseline to week 12 • Required dose of Binocrit® remained stable over the treatment period
Rodriguez Garzotto et al, Poster presented at the ECC Amsterdam, 2013	Binocrit® 40,000 IU (n=116) or 30,000 IU once weekly (n=14) Aranesp® 500 µg once every 3 weeks (n=99) Aranesp® 300 µg once every 2 weeks (n=2) Aranesp® 150 µg once weekly (n=45) NeoRecormon® 30,000 IU once weekly (n=8)	Patients with various solid tumours or haematological malignancies, in receipt of chemotherapy	• No significant difference between the treatment groups in: – Hb level at start of treatment – Hb level at end of treatment – Highest Hb achieved on treatment
Lorenz et al, Poster presented at the ECC Amsterdam, 2013	Binocrit® 40,000 IU once weekly (n=95) Aranesp® 500 µg once every 3 weeks (n=50)	Patients with various solid tumours in receipt of chemotherapy	• Once-weekly treatment with Binocrit® as effective as Aranesp® 500 µg once every 3 weeks for increasing Hb levels and avoiding the need for transfusions

Pharmacoeconomic considerations

It is estimated that biosimilar epoetins saved €551 million in Germany between 2007 and 2011 (Data source: .ZI AVD). A study by IGES Institute in Berlin estimates that healthcare systems in eight EU countries can save up to EUR 33 billion by 2020 through the introduction of biosimilars (Cost Savings from the use of biosimilars in the EU, Haustein et al 2012).

Another analysis across seven European countries (including the UK) calculated 2010 expenditure on epoetins in oncology to be US$1,117 million; assuming a 100% switch to a biosimilar epoetin (at 2010 prices), an annual saving of US$188 million would be realised [Aapro, *GaBI,* 2013]. Cost savings associated with biosimilars may increase access to treatment and/or be reinvested in the health economy.

Additional considerations

There are no studies designed for superiority demonstrating efficacy or safety benefits of long-acting compared with short-acting ESAs in terms of Hb correction or safety in cancer. Higher acquisition cost of long-acting ESAs may not always be justified by the proposed convenience benefit in some patients (e.g., those undergoing three-weekly chemotherapy cycles). In Europe, patients who receive ESAs for CIA frequently may self-administer treatment at home, and rarely require home nursing assistance. The costs associated with administering ESAs for CIA should therefore be assumed to be similar across all approved ESA products.
Modern manufacturing technologies confer purity and design benefits. Binocrit has an in-built needle safety guard and has an extended shelf-life compared to its originator [Binocrit Summary of Product Characteristics, 2012].