



European Medicines Agency
Evaluation of Medicines for Human Use

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**ASSESSMENT REPORT
FOR
EPOETIN ALFA HEXAL**

**International non-proprietary name/Common name:
epoetin alfa**

Procedure No. EMEA/H/C/725/II/0006

**Variation Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted**

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1.1. Introduction

Human erythropoietin is a glycoprotein which is produced primarily in the kidneys and promotes red blood cell production by stimulating the division and differentiation of committed progenitors in the bone marrow. Erythropoietin for clinical use is produced by recombinant DNA technology using mammalian cells as expression system.

Epoetin alfa Hexal (HX575) has been developed as a biosimilar product to the reference product Eprex/Erypo (epoetin alfa, Janssen-Cilag GmbH). The active substance for both products, is an epoetin of identical primary structure as the endogenous human erythropoietin and is produced in Chinese Hamster Ovary (CHO) cells.

Epoetin alfa Hexal is indicated for the treatment of:

- Treatment of anaemia associated with chronic renal failure in paediatric and adult patients on haemodialysis and adult patients on peritoneal dialysis (See section 4.4).
- Treatment of severe anaemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing dialysis (See section 4.4).

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).

Epoetin alfa Hexal 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.

Epoetin alfa Hexal is presented as a solution for injection. It is available in pre-filled syringes containing between 1,000 and 10,000 international units (IU) of the active substance, epoetin alfa. Epoetin alfa Hexal was approved as a biosimilar of Eprex/Erypo product in the European Union on 28 August 2007 with the same indications as the originator Erypo/Eprex with the exception of its use to increase the yield of autologous blood from patients in a predonation program, an indication protected by intellectual property rights until April 2008 in the EU.

1.2 Clinical aspects

Background

Erythropoietin is a glycoprotein which stimulates red blood cell production. It is produced in the kidney and stimulates the division and differentiation of erythroid progenitors in the bone marrow. Epoetin alfa, a 165 amino acid glycoprotein manufactured by recombinant DNA technology, has the same biological effects as endogenous erythropoietin. It is produced by mammalian cells into which the human erythropoietin gene has been introduced. Epoetin alfa contains the identical amino acid sequence of isolated natural erythropoietin.

Epoetin alfa has been shown to stimulate erythropoiesis in anaemic patients with chronic renal failure (CRF), including those on dialysis and those who do not require regular dialysis. In addition, severe anaemia caused by non-renal disease can be corrected or alleviated following treatment with epoetin alfa, e.g. in cancer patients on chemotherapy. Response to epoetin alfa in these patients is manifested by increased haematocrit, haemoglobin, reduced transfusion requirements and increase in quality of life. In patients with moderate anaemia undergoing major elective surgery accompanied by considerable blood loss, epoetin alfa can be used to increase the yield of autologous blood in a predonation program. Epoetin alfa treatment was shown to reduce the exposure to allogeneic blood transfusion in patients undergoing major elective orthopaedic surgery.

An application for a "Similar Biological Medicinal Product" via the centralised procedure under Article 10(4) of Directive 2001/83/EC as amended, also making reference to its Annex 1 was submitted to get marketing approval. The application was based on a comparability concept against the reference medicinal product Erypo® (Janssen-Cilag), as authorized in Germany which has been registered in Europe for more than 10 years. Marketing authorisation was issued by the European Commission on 28 August 2007. The drug substance epoetin alfa was originally developed by Amgen Inc. In the US, the drug substance is marketed as Epogen™ and Procrit™ and outside the US with a different composition under the brand name Eprex® or Erypo®. Details of the studies performed with HX575 are included in the scientific discussion section in the EPAR.

Discussion

The clinical development program of HX575 was in line with the *Guidance on Similar Medicinal Products Containing Recombinant Erythropoietins*, with one exception, i.e. the recommendation to provide results from at least two adequately powered, randomised, parallel group clinical trials demonstrating comparable efficacy and safety for both routes of administration in patients with renal anaemia. It was acknowledged by the CHMP that at the time of clinical development, Erypo®/Eprex® could not be used as comparator in s.c. studies in renal anaemia patients and therefore no second randomised, parallel-group clinical trial with the s.c. route of application could be conducted. Under these circumstances, the deviation from the guideline was considered to be acceptable (EPAR Epoetin alfa Hexal®). A justification for extrapolation to the indication "increasing the yield of autologous blood from patients in pre-donation program" of the reference product Erypo®/Eprex® is given below based on following arguments:

1) Extrapolation is justified based on Biosimilar Concept

The MAH developed HX575 as a "Similar Biological Medicinal Product" with Erypo®/Eprex® (Janssen Cilag) as reference product via the centralised procedure under Article 10(4) of Directive 2001/83/EC as amended.

As such, the statement that the "demonstration of efficacy and safety in renal anaemia may allow extrapolation to other indications of the reference medicinal product if appropriately justified by the applicant" of EMEA *Guidance on Similar Medicinal Products Containing Recombinant Erythropoietins (Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues, EMEA/CHMP/BMWP/94526/2005 Corr.)* applies.

2) Extrapolation is justified based on biosimilar PK/PD data on Epoetin alfa Hexal

The PK/PD profile of HX575 and Erypo®/Eprex® is similar following administration of low or high doses and by both i.v. and s.c route of administration. These findings were observed in a population of healthy volunteers, a population which is relevant for the claimed pre-operative autologous donation (PAD) indication. For a detailed outline of the the two pivotal Phase I studies performed during development to show biosimilarity between HX575 and Erypo®/Eprex®.

3) Extrapolation is justified based on equivalent efficacy and safety data

Appropriate demonstration of equivalent efficacy and safety of HX575 to Erypo®/Eprex® has been shown during development in two phase III studies. Based on these data establishing HX575 to be efficacious and safe in renal anaemia and chemotherapy-induced anaemia, no additional clinical studies need to be performed in the pre-operative autologous blood donation indication to extend this indication of Erypo®/Eprex® to HX575.

4) Extrapolation is justified based on the same mode of action

According to EMEA *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues* (EMEA/CHMP/BMWP/42832/2005) justification needs to be provided when extrapolating from one to another indication. Such justification "will depend on e.g. clinical experience, available literature data, whether or not the same mechanisms of action or the same receptor(s) are involved in all

indications". The mechanism of action of EPO is identical regardless of disease state or route of administration

Therefore, given that: i) the mechanism of action of EPO is identical regardless of disease state or route of administration; ii) the PK/PD profile following administration of low or high doses of HX575 and Erypo[®]/Eprex[®] by both i.v. and s.c. routes are similar; and iii) appropriate demonstration of efficacy and safety in renal anaemia has been shown for HX575, no additional clinical study needs to be performed to claim an extension indication for increasing the yield of autologous blood from patients in pre-donation program.

In the submitted marketing authorisation dossier, the MAH provided results from five pharmacokinetic/pharmacodynamic studies performed in healthy volunteers and investigating single or multiple 100 IU/kg (per week) doses. The MAH has also provided efficacy and safety results from two double blind, randomised, parallel-group, multicenter phase III studies. Study INJ-9 was designed to evaluate a 1:1 conversion from Eprex/Erypo to HX 575 with respect to efficacy based on haemoglobin assessment in CRF patients on haemodialysis. Study INJ-11 was performed in patients receiving chemotherapy for solid tumours. The primary objective was to assess the efficacy and safety of HX 575 in the treatment of chemotherapy-associated anaemia. An Eprex/Erypo-treated group was included as internal control only. The clinical development programme was not in line with the guideline on similar biological medicinal products containing recombinant erythropoietins or previous scientific advice which notably recommended to provide results taken from at least two adequately powered, randomised, parallel group clinical trials demonstrating comparable efficacy and safety for both routes of administration in patients with renal anaemia. It is acknowledged, however, that at the time of clinical development EPREX/ERYPO could not be used as comparator in SC studies in renal anaemia patients due its contraindication.

Since the mechanism of action of EPO is identical regardless of disease state or route of administration, the PK/PD profile following administration of low or high doses of HX575 and Erypo[®]/Eprex[®] by both i.v. and s.c. routes are considered as similar. Since demonstration of efficacy and safety in renal anaemia has been shown for HX575, the MAH believes that no additional clinical study needs to be performed. Therefore, the Company claims an extension indication for increasing the yield of autologous blood from patients in pre-donation programme.

SPC Changes

4.1 Therapeutic indications

[...]

Epoetin alfa Hexal can be used to increase the yield of autologous blood from patients in a pre-donation 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) 10–13g/dl [6.2–8.1 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).

[...]

4.2 Posology and method of administration

[...]

Treatment of patients with chemotherapy induced anaemia:

Adult surgery patients in an autologous pre-donation programme:

Epoetin alfa Hexal should be given by the intravenous route.

At the time of donating blood, Epoetin alfa Hexal should be administered after the completion of the blood donation procedure.

Mildly anaemic patients (haematocrit of 33 - 39%) requiring predeposit of ≥ 4 units of blood should be treated with Epoetin alfa Hexal at a dose of 600 IU/kg body weight 2 times weekly for 3 weeks prior to surgery.

All patients being treated with Epoetin alfa Hexal should receive adequate iron supplementation (e.g. 200 mg oral elemental iron daily) throughout the course of treatment. Iron supplementation should be started as soon as possible, even several weeks prior to initiating the autologous predeposit, in order to achieve high iron stores prior to starting Epoetin alfa Hexal therapy.

[...]

4.3 Contraindications

[...]

Uncontrolled hypertension.

In the indication “increasing the yield of autologous blood”: myocardial infarction or stroke in the month preceding treatment, unstable angina pectoris, increased risk of deep venous thrombosis such as history of venous thromboembolic disease.

[...]

4.4 Special warnings and precautions for use

[...]

Adult cancer patients with symptomatic anaemia receiving chemotherapy

[...]

Adult surgery patients in an autologous predonation programme

All special warnings and precautions associated with autologous predonation programmes, especially routine volume replacement, should be respected.

[...]

4.6 Pregnancy and lactation

[...]

- In pregnant or lactating surgical patients participating in an autologous blood predonation programme, the use of epoetin alfa is not recommended.

[...]

4.8 Undesirable effects

[...]

Surgery patients in autologous predonation programmes

Independent of erythropoietin treatment, thrombotic and vascular events may occur in surgical patients with underlying cardiovascular disease following repeated phlebotomy. Therefore, routine volume replacement should be performed in such patients.

[...]

Package Leaflet

1. WHAT EPOETIN ALFA HEXAL IS AND WHAT IT IS USED FOR

[...]

in moderately anaemic patients who are going to have surgery and prior to it, donate blood so that their own blood can be given to them during or after surgery (autologous predonation)

[...]

2. BEFORE YOU USE EPOETIN ALFA HEXAL

Do not use Epoetin alfa Hexal:

[...]

- if you are donating your own blood before surgery, and:
you had a heart attack or stroke in the month before your treatment
you have unstable angina pectoris (new or increasing chest pain)
you are at risk of blood clots in the veins (deep venous thrombosis) – for example, if you have had clots before

[...]

Cancer patients

If you are a cancer patient you should be aware that Epoetin alfa Hexal may act as a blood cell growth factor and in some circumstances may have a negative impact on your cancer. Depending on your individual situation a blood transfusion may be preferable. Please discuss this with your doctor.

Patients donating their own blood before surgery

Your doctor will consider warnings and precautions associated with autologous blood predonation, especially volume replacement.

[...]

4. POSSIBLE SIDE EFFECTS

[...]

Patients donating their own blood before surgery with underlying cardiovascular disease: after donating blood repeatedly vascular and thrombotic events (blood clotting) can occur independently of treatment with Epoetin alfa Hexal. Therefore your doctor may prescribe a medicinal product for volume replacement (infusion).

[...]

2. CONCLUSION

On 23 October 2008 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Labelling and Package Leaflet.