EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 July 2018
EMA/CHMP/549796/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMEA/H/C/WS1406

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name/Common name:	Product-specific application number
Abseamed	epoetin alfa	EMEA/H/C/000727/WS1406/0070
Binocrit	epoetin alfa	EMEA/H/C/000725/WS1406/0070
Epoetin alfa Hexal	epoetin alfa	EMEA/H/C/000726/WS1406/0069

Worksharing applicant (WSA): Sandoz GmbH

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
CKD	Chronic Kidney Disease
CRF	Chronic Renal Failure
DAR	Darbepoetin
DHPC	Direct Healthcare Professional Communication
EC	Commission Regulation
EEA	European Economic Area
EPO	Erythropoietin
ESMO	European Society of Medical Oncology
ESA	Erythropoiesis-stimulating agent
EU	European Union
EMA	European Medicines Agency
EPAR	European Public Assessment Report
g	Gram
GVP	Guideline on Good Pharmacovigilance Practices
Hb	Hemoglobin
HX575	Binocrit/Epoetin alfa HEXAL/Abseamed
ICSRs	individual case safety reports
IU	UseInternational units
i.v.	Intravenous
kg	Kilogram
L	Liter
MAH	Marketing Authorization Holder
MA	Marketing authorization
MDS	Myelodysplastic syndrome
mL	Milliliter
mmol	Micromol
N/A	Not Applicable
NCCN	National Comprehensive Cancer Network
PASS	Post-Authorization Safety Study
PFS	Pre-Filled Syringe
PK	Pharmacocinetic
PD	Pharmacodynamic
PL	Package Leaflet
PRCA	Pure Red Cell Aplasia
PSUR	Periodic Safety Update Report
PL	Package leaflet
RBCs	Red Blood Cells
RMP	Risk Management Plan
SCARs	Severe Cutaneous Adverse Reactions
SmPC	Summary Product Caracteristics
SJS	Stevens Johnson Syndrome
s.c	Subcutaneous
TEN	Toxic Epidermal Necrolysis
WSA	Worksharing applicant

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sandoz GmbH submitted to the European Medicines Agency on 3 May 2018 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.2.b	C.I.2.b - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Change(s) require to be further substantiated by new additional data to be submitted by the MAH	Type II	I, IIIA, IIIB and A

Extension of indication to include the treatment of symptomatic anaemia (haemoglobin concentration of ≤ 10 g/dl) in adults with low- or intermediate-1-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin (< 200 mU/ml) for Binocrit, Epoetin alfa Hexal and Abseamed; as a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated with safety and efficacy information. The Package Leaflet and the risk management plan (version 17.0) are updated in accordance. In addition, the worksharing applicant (WSA) took the opportunity to align information with the reference medicinal product and with the EC guideline on Excipients, to improve the quality and readability of the translations in the product information and to update the Annex A in line with EMA guideline.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics, Labelling, Package Leaflet and Annex A and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Appointed (Co-)Rapporteurs for the WS procedure:

Alexandre Moreau

Timetable	Actual dates
Submission date	3 May 2018
Start of procedure:	28 May 2018
CHMP Rapporteur Assessment Report	27 June 2018
PRAC members comments	N/A
PRAC Outcome	12 July 2018
CHMP members comments	16 July 2018
Updated CHMP Rapporteur Assessment Report	19 July 2018
Opinion	26 July 2018

2. Scientific discussion

2.1. Introduction

Binocrit/Abeseamed/Epoetin Hexal alfa (HX575) is developed by Sandoz GmbH for the treatment of patients with anaemia. The active substance of HX575 is epoetin alfa, a recombinant protein expressed in Chinese hamster ovary cells whose amino acid sequence is identical to human urinary glycoprotein hormone erythropoietin (EPO), and is supposed to be functionally indistinguishable from endogenous human EPO. EPO is a growth factor produced primarily by the kidney in response to hypoxia that stimulates red blood cell production. EPO receptors may be expressed on the surface of a variety of tumour cells.

HX575 in pre-filled syringes (PFS) is a biosimilar epoetin alfa product to Erypo/Eprex. It was originally approved in Aug 2007 and a renewal was obtained in June 2012. Based on the totality of the evidence, biosimilarity between HX575 and the reference product was established in the original development program, in terms of similar physicochemical and biological/functional properties, similar clinical PK and PD profiles, efficacy and safety data.

Current indications

Binocrit is indicated for the treatment of symptomatic anaemia associated with chronic renal failure (CRF):

in adults and children aged 1 to 18 years on haemodialysis and adult patients on peritoneal dialysis (see section 4.4).

in adults with renal insufficiency not yet undergoing dialysis for the treatment of severe anaemia of renal origin accompanied by clinical symptoms in patients (see section 4.4).

Binocrit is indicated in adults 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) for the treatment of anaemia and reduction of transfusion requirements.

Binocrit is indicated in adults in a predonation programme to increase the yield of autologous blood. Treatment should only be given to patients with moderate anaemia (haemoglobin [Hb] concentration range

between 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).

Binocrit is indicated for non-iron deficient adults prior to major elective orthopaedic surgery, having a high perceived risk for transfusion complications to reduce exposure to allogeneic blood transfusions. Use should be restricted to patients with moderate anaemia (e.g. haemoglobin concentration range between 10 to 13 g/dl or 6.2 to 8.1 mmol/l) who do not have an autologous predonation programme available and with expected moderate blood loss (900 to 1,800 ml).

Proposed additional indication

Binocrit is indicated for the treatment of symptomatic anaemia (haemoglobin concentration of ⩽10 g/dl) in adults with low- or intermediate-1-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin (< 200 mU/ml).

Myelodyplasic syndrome disease

Myelodysplastic syndromes comprise a group of clinically heterogeneous clonal bone marrow stem cell disorders. MDS is characterized by ineffective hematopoiesis, cytopenias (particularly anemia), and cellular dysfunctions. Cytopenias may eventually cause other symptoms, including asthenia and dyspnea as a result of anemia. Risk of infections may result from neutropenia, and bruising or spontaneous bleeding may result from thrombocytopenia. The natural course of MDS is highly variable, with overall survival ranging from a few weeks to several years due to various prognostic subtypes. MDS is primarily a disease of the elderly, with a median age at diagnosis of 70 years. The incidence in Europe is approximately 4 cases per 100,000 per year, reaching 40-50 per 100,000 in patients aged 70 years and older.

Rationale proposed change

Approximately 60-80 percent of the patients with MDS experience symptomatic anemia, which can significantly reduce quality of life and increase morbidity, and often requires repeated blood transfusions. Controlling anemia and improving quality of life are the principal aims of treatment in lower risk MDS patients, while in the intermediate and high risk groups the goal is rather the prevention of complications of other severe cytopenias, or even reduction in MDS potential for leukemic evolution. Until recently, no vitamin supplementation was effective for MDS patients presenting mostly as anemic. RBC transfusions have until recently been the only approved treatment option and limited to the anemia component of MDS; however, these carry the risk of immunogenicity and iron overload, which are known to be associated with significant morbidity and mortality.

In 2014 the European Society of Medical Oncology (ESMO) Guideline for MDS treatment recommended ESAs for the treatment of anemia associated with low risk MDS, especially with low serum epoetin level. The recent National Comprehensive Cancer Network (NCCN) Guideline for MDS treatment (2018) in the US now also supports the use of ESAs, including epoetin alfa as initial treatment in low risk MDS without 5q partial chromosomal deletion and with low serum epoetin level.

The MAH indicated that this variation application is in agreement with the following EMA guidelines:

- Guideline on similar biological medicinal products (EMEA/CHMP/437/04 Rev. 1). In which is reported that:"If biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification."
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev. 1). This guideline mentioned that: "In case the reference medicinal product has more than one therapeutic indication, the efficacy and safety of the biosimilar has to be justified or, if necessary, demonstrated

separately for each of the claimed indications. Justification will depend on, e.g., clinical experience, available literature data, mechanisms of action of the active substance of the reference product in each indication (including its degree of certainty), and on receptors iinvolved."

Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins (Revision) (EMEA/CHMP/BMWP/301636/2008 Corr.). This guideline mentioned that "Since the mechanism of action of epoetin is the same for all currently approved indications and there is only one known epoetin receptor, demonstration of efficacy and safety in renal anaemia will allow extrapolation to other indications of the reference medicinal product with the same route of administration."

2.2. Clinical efficacy

2.2.1. Methods and results

The applicant provided a scientific justification for extrapolation of indication in the following sections.

- **Mode of action of epoetin alfa**

Epoetin is a glycoprotein hormone produced primarily by the kidney in response to hypoxia; it is a key regulator of the production of red blood cells (RBCs). Epoetin is involved in all phases of erythroid development in the bone marrow, and has its principal effect at the level of erythroid precursors. Epoetin binds to its cell surface receptor and activates signal transduction pathways that interfere with apoptosis and also stimulates erythroid cell proliferation. Recombinant human epoetin alfa is an ESA that works by stimulating the production of RBCs mimicking the physiological action of the endogenous hormone. The mode of action of epoetin alfa is the same for all approved indications and there is only one known epoetin receptor (EMEA/CHMP/BMWP/301636/2008 Corr.), whether to correct anaemia in various indications with different corresponding doses, or to protect from future anaemia in pre-surgery indications.

- **Biosimilarity between HX575 and the reference product**

HX575 in pre-filled syringes (PFS) is a biosimilar epoetin alfa product to Erypo/Eprex. The first commercially available recombinant epoetin was epoetin alfa/Eprex. Based on the totality of the evidence, biosimilarity between HX575 and the reference product was established in the original development program, in terms of similar physicochemical and biological/functional properties, similar clinical PK and PD profiles, efficacy and safety data. Based on this, the MA was initially granted in the following indications:

- for the treatment of symptomatic anaemia associated with chronic renal failure
- for the treatment of chemotherapy-induced anaemia and reduction of transfusion requirements
- for surgery patients in an autologous blood donation program
- for patients scheduled for orthopaedic surgery.

- **Key efficacy results of the EPOANE 3021 study conducted with the reference product in MDS patients**

Study EPOANE 3021 was a randomized 1:2, double-blind, placebo-controlled, multicentre clinical trial investigating the efficacy and safety of Eprex as a treatment for anemia in adult patients with low or intermediate-1-risk MDS, as classified by an International Prognostic Scoring System. Results showed that 31.8% of the 85 patients treated with epoetin alfa achieved the primary endpoint of erythroid response (per International Working Group 2006 response criteria) lasting at least 8 weeks by Week 24, compared with 4.4% of the 45 patients treated with placebo ($p<0.001$).

An ad-hoc analysis of the erythroid response time distribution over the total 52 weeks study duration was conducted by a Response Review Committee and confirmed a statistically significant difference between

treatment groups, with 45.9% of the patients in the epoetin alfa group achieving an erythroid response compared with 4.4% of the patients in the placebo group (p<0.001). The analysis also showed that all responding patients had low serum epoetin <200 IU/mL, and that higher proportions of responders were found among patients with lower prognostic risk and with lower pre-treatment transfusion needs.

The mean erythroid response duration for patients treated with epoetin alfa was 192.3 days, with a median weekly dose of 730.4 IU/kg over 24 weeks. The number of patients requiring transfusion in the epoetin alfa group steadily decreased from 51.8% in the 8 weeks prior to baseline to 24.7% by Week 24. Transfusion need remained unchanged in patients treated with placebo (48.9% to 54.1%) over 24 weeks. The time to first transfusion was significantly longer in the epoetin alfa group (p=0.046). Epoetin alfa treatment also showed a statistically significant improvement of quality of life in responding patients (EPOANE 3021 Clinical Study Synopsis).

2.2.2. Discussion

This Application is a type II variation to extend the indications of HX575 to the treatment of symptomatic anaemia (haemoglobin concentration of 10≤ g/dL= in adult with low- or intermediate- 1 risk primary myelodysplastic syndromes (MDS) and low serum erythropoietin (<200 IU/mL). This last indication was approved for the originator product (Eprex/Erypo) through the Mutual Recognition Procedure with France acting as RMS in 2017.

The initial originator Application was mainly based on the EPOANE 3021 study. Since the exclusivity protection for EPOANE 3021 data has been granted for the period of one year, the MAH is submitting a type II variation after the one-year exclusivity being expired.

This variation is overall in agreement with the following EMA guidelines:

- guideline on similar biological medicinal products (EMEA/CHAMP/437/04 Rev. 1).
- guideline on similar medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHAMP/BMWP/42832/2005 Rev. 1).
- guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropietins (Revision) (EMEA/CHMP/BMWP/301636/2008 Corr.).

According to guideline on similar biological medicinal products, biosimilarity between HX575 and the reference product has been already demonstrated in at least one pivotal indication. The scientific justification provided to extrapolate the biosimilary to the other indication is appropriate.

Overall, the efficacy and safety of HX575 is justified by the mechanism of action of the active substance of the reference product which is the same in each approved indication. Consequently, the efficacy and safety similarity which was mainly demonstrated in renal anaemia patients allow an extrapolation to the extension of indication of the reference medicinal product with the same route of administration.

2.3. Clinical safety

2.4. Methods and results

- **Overview of safety – post-marketing safety data**

HX575 is currently approved in all countries of European Economic area (EEA). It has since received marketing authorization in 37 non EEA countries via national registration.

The extensive post-marketing safety data of HX575 as compiled in Sandoz's global safety database are estimated to cover 283,227,200 patient-days (by 31-Aug-2017). Based on the post-marketing data sources

such as spontaneous individual case safety reports (ICSRs), including reports from healthcare professionals, consumers, scientific literature, and competent authorities (worldwide) and from solicited non-interventional ICSRs including those from non-interventional studies, it can be concluded that the safety profile of HX575 remains to be positive and in line with the previous cumulative experience and the safety information provided in the reference safety information for erythropoietin.

The recent PSUR version 11.0 reported that the benefit/risk assessment remains favourable. The RMP provided with this type II variation was updated. Further details on these and on safety data from the EU HX575-507 Post-Authorization Safety Study (PASS) study in chronic kidney disease (CKD) patients (currently ongoing) and the EPOANE 3021 study in MDS patients are provided throughout below. The MAH reported that the routine pharmacovigilance activities will continue upon approval of treatment with HX575 in MDS patients.

Information on reported adverse events (including deaths and serious adverse events) is regularly collected and assessed by Sandoz for all marketed epoetin alfa products (including originator and other biosimilar products, and not only those marketed by Sandoz). Relevant publications containing important new safety information associated with erythropoietin are also reviewed in PSURs. During the review period of PSUR 11.0, there were no articles concerning new and significant safety findings, pregnancy, compassionate supply and named patient use, lack of efficacy, overdose, abuse of misuse, medication error, and non-clinical use.

The established safety profile of the approved indications of HX575 is summarized in the Binocrit: EPAR – Product Information. Contraindications, special warnings and precautions for use are essentially the same as for Erypo/Eprex. No new or unknown adverse events for the class of drug were observed for HX575. Undesirable effects are described in Section 4.8 of the current SmPC.

- **Study HX575-507 and antibody-induced pure red cell aplasia (PRCA)**

Currently epoetins alfa products are marketed by Sandoz in the EU for several indications. PRCA has been previously identified as a safety concern with subcutaneous usage in chronic kidney disease patients. Since March 2016, HX575 has been authorized for the s.c. route of administration in patients with CKD-induced anemia (in addition to the i.v. mode of administration).

To further collect safety data of HX575 and to fulfil the post approval commitment, the Non-Interventional Post-Authorization Safety Study (NI-PASS) HX575-507 was initiated in 2017 as appropriate measure to identify any risk associated with the s.c. administration route of HX575 in CKD patients under real-life post-approval conditions, including PRCA risk, a known treatment effect of the reference product.

This NI-PASS study concept was discussed and agreed upon with the EMA in March 2016 and is part of the EU RMP. This is in addition to the standard pharmacovigilance reporting, which will include the reporting of potential antibody-induced PRCA cases. The study will report the safety data of 2500 patients over 24 months with HX575 s.c. treatment.

Spontaneous reports of 10 cases of antibody-induced PRCA with the marketed product were received until 31-Aug-2017. Antibody-mediated PRCA has been reported after months to years of subcutaneous epoetin treatment mainly in chronic renal failure patients. Causality assessment in these cases is hampered by limited information and confounding factors.

Cases of PRCA in patients with hepatitis C virus treated with interferon are known from the literature[1]. The current Company Core Data Sheet states that cases have also been reported in patients with hepatitis C treated with interferon and ribavirin, when ESAs are used concomitantly. Epoetin alpha is not approved in the management of anaemia associated with hepatitis C.

[1] Rossert J, Yue S, Smirnakis K, et al (2014)] Risk of pure red cell aplasia in patients with C receiving antiviral therapy and an erythropoiesis-stimulating agent. Clin Gastroenterol Hepatol; 12(2):341-5.

- **Studies HX575-307 and HX575-308**

Two clinical trials were recently conducted with HX575 s.c. in CKD patients with anemia; both were completed in Oct 2014.

Study HX575-308 was conducted in Europe and assessed the incidence of antibody formation against HX575 (s.c. administration), thus furthering the safety profile of HX575. Study HX575- 308 was a single arm prospective multicenter study conducted in Europe with the primary objective to evaluate the safety and the immunogenicity of HX575 (s.c. administration; HX575 low-tungsten syringes) over 52 weeks, thus furthering the safety profile of HX575 in 416 patients.

Study HX575-307 investigated the incidence of antibody formation against HX575 and the safety profile of HX575 compared to the US-licensed epoetin alfa Epogen/Procrit (in vials; product not approved in Europe, designed for US). Study HX575-307 was a 1:1 randomized study in the US in 435 patients with dialysis, comparing the s.c. administration of HX575 to the US-licensed epoetin alfa Epogen/Procrit (in vials; designed for US). The primary objective of the study was to demonstrate equivalence in efficacy at the end of the initial anemia correction period, and also to evaluate the incidence of antibody formation against HX575 and the safety profile over 52 weeks.

No NAbs or PRCAs were detected in either study.

2.5. Discussion

HX575 is currently approved in all countries of European Economic area (EEA). It has since received marketing authorization in 37 non EEA countries via national registration.

The extensive post-marketing safety data of HX575 as compiled in Sandoz's global safety database are estimated to cover 283,227,200 patient-days (by 31-Aug-2017). Based on the post marketing data sources such as spontaneous individual case safety reports (ICSRs), including reports from healthcare professionals, consumers, scientific literature, and competent authorities (worldwide) and from solicited non-interventional ICSRs including those from non-interventional studies, it can be concluded that the safety profile of HX575 remains to be positive and in line with the previous cumulative experience and the safety information provided in the reference safety information for erythropoietin.

PRCA has been previously identified as a safety concern with subcutaneous usage of epoetins alfa in chronic kidney disease patients. HX575 has been authorised for s.c. route of administration in patients with CKD induced anaemia. The Non-Interventional Post-Authorization Safety Study (NI-PASS) HX575-507 was initiated in 2017 as appropriate measure to identify any risk associated with the s.c. administration route of HX575 in CKD patients under real-life post-approval conditions, including PRCA risk, a known treatment effect of the reference product. This NI-PASS study concept is part of the EU RMP.

In the frame of the new indication, the RMP provided and the section 4.8 of the SmpC were updated accordingly.

2.6. Risk management plan

The MAH has submitted updated RMP version 17.0 in order:

- to include the new indication of symptomatic anaemia in patients with low or intermediate-1-risk MDS;
- to include the Direct Healthcare Professional Communication (DHPC) on severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN);

- to be in line with the current “Guideline on good pharmacovigilance practices (GVP) Module V – Risk Management systems” and the “Guidance on format of the risk management plan (RMP) in the EU” effective on 31 Mar 2017.

The DHPC regarding the risk of SCARs including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) with epoetins was punctually disseminated to healthcare professionals on September 2017 (EPITT No 18846, adoption of PRAC recommendation on 6th July 2017). Additionally, as part of final PRAC recommendation of the EPITT signal, this risk was implemented in sections 4.4 and 4.8 of the EU-SmPC of epoetin alpha containing products (including Binocrit). Therefore, at this time, the SCARs associated with epoetin alpha have been well established and characterised and no further characterisation by additional risk minimisation measures or pharmacovigilance activities is needed. As a result, the MAH updated the RMP (finally agreed version 17.1) and removed SCARs and the associated DHPC from the content of the RMP.

New text marked as underlined, deletions marked as strikethrough:

Safety concerns

Summary of safety concerns	
Important identified risks	Pure Red Cell Aplasia (PRCA) Thromboembolic events Hypertension/hypertensive crisis Seizure Premature death Hypersensitivity reactions (including anaphylactic reactions) Hyperkalemia ~~Severe cutaneous adverse reactions (SCARs)~~
Important potential risks	Tumor growth potential Congestive heart failure Misuse
Missing information	Safety in pregnancy and lactation Safety in children

Pharmacovigilance plan

Study / Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				

Study / Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
NIS-PASS (MEA 13.5) Ongoing	To increase further confidence in the real world of the safe and efficacious use of Sandoz epoetin alfa administered subcutaneously in patients with CKD associated anemia, especially with regards to PRCA and loss of efficacy. The study primary objective is to evaluate rare AEs like PRCA and other AEs of special interest	PRCA and other rare AEs of special interest, overall safety of HX575 in s.c. administration in CKD patients	Study start date Analyses after 1000 and 2500 patients enrolled Final report (planned)	12 Apr 2017 N/A: upon completion of 2500 subjects and data analysis Feb 2023. Twelve months after end of data collection
TRIGONS study MEA 18; HX575-502 pharmacoepidemiological study MEA 18 is related to LEG027/028. Not applicable/Pending EMA decision.	To evaluate the within-treatment and long-term safety of de novo treatment with HX575 or RBC transfusion for managing chemotherapy induced anemia in ovarian cancer patients.	Thrombotic events Tumor growth potential	Pending EMA decision. In Assessment report dated Jan 2014 the CHMP agreed to wait for the results of currently ongoing clinical and non-clinical studies by Amgen and Roche respectively before deciding on further steps.	N/A

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Pure Red Cell Aplasia (PRCA)	Routine risk minimization measures: SmPC Sections 4.3, 4.4, 4.8. PL Section 2 Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: NIS-PASS (MEA 13.5)
Thromboembolic events	Routine risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions reporting

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC Sections 4.3, 4.4, 4.8 and 5.1. PL Section 3. Legal status: Prescription only	and signal detection: None Additional pharmacovigilance activities: TRIGONS study, study MEA 18; HX575-502, pharmacoepidemiological study, MEA 18 is related to LEG027/028
Hypertension/hypertensive crisis	Routine risk minimization measures: SmPC Sections 4.3, 4.4, 4.8 PL Section 3. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Seizure	Routine risk minimization measures: SmPC Sections 4.4, 4.8 Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Premature death	Routine risk minimization measures: SmPC Sections 4.4, 4.8 and 5.1. PL Section 2. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Hypersensitivity reactions (including anaphylactic reactions)	Routine risk minimization measures: SmPC Sections 4.3 and 4.8. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Hyperkalemia	Routine risk minimization measures: SmPC Sections 4.4 , 4.8. PL Section 3. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
~~Severe cutaneous adverse reactions (SCARs)~~	~~Routine risk minimization measures:~~ ~~SmPC Sections 4.4 , 4.8.~~ ~~PL Section 2~~ ~~Legal status: Prescription only~~ ~~Additional risk minimization measures: DHPC~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None~~ ~~Additional pharmacovigilance activities: None~~
Important potential risks		
Tumor growth potential	Routine risk minimization measures: SmPC Sections 4.4, 4.5, 5.1 and 5.3 Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Congestive heart failure	Routine risk minimization measures: SmPC Section 5.1 PL Section 2. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Misuse	Routine risk minimization measures: SmPC section: None PL section: None Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing information		
Safety in pregnancy and lactation	Routine risk minimization measures: SmPC Section 4.6 PL Section 2 Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Safety in children	Routine risk minimization measures: SmPC Section 4.8 PL section: None Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 17.1 is acceptable provided that the revision of the list of safety concerns as per new RMP template Rev.2 should be done by the MAH as a post approval commitment (at the next regulatory opportunity or within 6 months at the latest after opinion).

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.4 and 4.8 of the SmPC are being. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

3. Benefit-Risk Balance

HX575 is a biosimilar medicinal product. A MA was granted in August 2007 under the brand names Binocrit, Epoetin alfa HEXAL, and Abseamed.

This Application is a type II variation to extend the indications of HX575 to the treatment of symptomatic anaemia (haemoglobin concentration of 10≤ g/dL= in adult with low- or intermediate- 1 risk primary myelodysplastic syndromes (MDS)and low serum erythropoietin (<200 IU/mL). This last indication was approved for the originator product (Eprex/Erypo) through the Mutual Recognition Procedure with France acting as RMS in 2017.

The initial originator Application was mainly based on the EPOANE 3021 study. Since the exclusivity protection for EPOANE 3021 data has been granted for the period of one year starting from the 27th of April 2017, the MAH is submitting a type II variation after the one-year exclusivity being expired.

This variation is overall in agreement with the following EMA guidelines:

- guideline on similar biological medicinal products (EMEA/CHAMP/437/04 Rev. 1).
- guideline on similar medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHAMP/BMWP/42832/2005 Rev. 1).
- guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropietins (Revision) (EMEA/CHMP/BMWP/301636/2008 Corr.).

According to guideline on similar biological medicinal products, biosimilarity between HX575 and the reference product has been already demonstrated in at least one pivotal indication. The scientific justification provided to extrapolate the biosimilary to the other indication is appropriate.

Overall, the efficacy and safety of HX575 is justified by the mechanism of action of the active substance of the reference product which is the same in each approved indication. Consequently, the efficacy and safety similarity which was mainly demonstrated in renal anaemia patients allow an extrapolation to the extension of indication of the reference medicinal product with the same route of administration.

The RMP is updated to include the new indication and to remain in line with the current “guideline on good pharmacovigilance practices (GVP) module V- risk management systems” and the “guidance on format of risk management plan (RMP) in the EU”.

The DHPC regarding the risk of SCARs including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) with epoetins was punctually disseminated to healthcare professionals on September 2017 (EPITT No 18846, adoption of PRAC recommendation on 6th July 2017). Additionally, as part of final PRAC recommendation of the EPITT signal, this risk was implemented in sections 4.4 and 4.8 of the EU-SmPC of epoetin alpha containing products (including Binocrit). Therefore, at this time, the SCARs associated with epoetin alpha have been well established and characterised and no further characterisation by additional risk minimisation measures or pharmacovigilance activities is needed. As a result, the MAH updated the RMP (finally agreed version 17.1) and removed SCARs and the associated DHPC from the content of the RMP.

Moreover, the MAH submitted the EU-RMP v17.0 (and finally agreed version 17.1) supposed to be in line with the new GVP module V rev 2. Please note that substantial change was provided regarding the definition of important identified/potential risks in GVP module V rev 2. The revision of the list of safety concerns as per new template should be done by the MAH as a post approval commitment (at the next regulatory opportunity or within 6 months at the latest after opinion).

In conclusion, the overall benefit-risk balance of HX575 in the treatment of symptomatic anaemia (haemoglobin concentration of 10≤ g/dL= in adult with low- or intermediate- 1 risk primary myelodysplastic syndromes (MDS)and low serum erythropoietin (<200 IU/mL), is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.2.b	C.I.2.b - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Change(s) require to be further substantiated by new additional data to be submitted by the MAH	Type II	I, IIIA, IIIB and A

Extension of indication to include the treatment of symptomatic anaemia (haemoglobin concentration of ≤ 10 g/dl) in adults with low- or intermediate-1-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin (< 200 mU/ml) for Binocrit, Epoetin alfa Hexal and Abseamed; as a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated with safety and efficacy information. The Package Leaflet and the risk management plan (finally agreed version 17.1) are updated in accordance. In addition, the worksharing applicant (WSA) took the opportunity to align information with the reference medicinal product and with the EC guideline on Excipients, to improve the quality and readability of the translations in the product information and to update the Annex A in line with EMA guideline.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include the treatment of symptomatic anaemia (haemoglobin concentration of ≤ 10 g/dl) in adults with low- or intermediate-1-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin (< 200 mU/ml) for Binocrit, Epoetin alfa Hexal and Abseamed; as a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated with safety and efficacy information. The Package Leaflet and the risk management plan (finally agreed version 17.1) are updated in accordance. In addition, the worksharing applicant (WSA) took the opportunity to align information with the reference medicinal product and with the EC guideline on Excipients, to improve the quality and readability of the translations in the product information and to update the Annex A in line with EMA guideline.

Summary

Please refer to Scientific Discussion Abseamed-H-C-WS-1406, Binocrit-H-C-WS-1406, Epoetin alpha Hexal-H-C-WS-1406