SANDOZ A Novartis Division

Chief Medical Office & Patient Safety

Epoetin alfa
16.8 µg/ml, 84 µg/ml and 336 µg/ml
Solution for Injection

HX575-182-967-16-0

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Epoetin alfa
Product(s) concerned (brand name(s)):	Abseamed®, Binocrit®, Epoetin alfa Hexal®
Document status:	Final
Version number of the RMP Public Summary:	16.0
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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them. The RMP summary of Abseamed®, Binocrit®, Epoetin alfa Hexal® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Note that the reference document that is valid and relevant for the effective and safe use of Binocrit® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Sandoz Pharmaceuticals AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Binocrit®.

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Table 1-1 Part VI.1.1 Summary table of safety concerns

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	Thromboembolic events
	Hypertension / Hypertensive crisis
	Seizure
	Premature death
	Hypersensitivity reactions (including anaphylactic reactions)
	Hyperkalemia
Important potential risks	Tumor growth potential
	Congestive heart failure
	Misuse
Missing information	Safety in lactation
	Safety in children

Table 1-2 Part VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final Reports (planned or actual)
NIS-PASS (MEA 13.5) (category 3)	Non-interventional Post-Approval Safety Study, reporting the safety data of 2500 patients over 24 months s.c. HX575 treatment	Development of anti-epoetin antibodies (immunogenicity, PRCA)	Planned	To be determined
TRIGONS (MEA 18.3) (category 3)	Study to monitor safety in ovarian cancer patients suffering from chemotherapy induced anemia	To address thromboembolic morbidity, tumor progression and general and specific mortality in ovarian cancer patients	Planned	EMA decision pending

Table 1-3 Part VI.1.3 Summary of Post authorization efficacy development plan

N/A

Table 1-4 Part VI.1.4 Summary table of risk minimization measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Pure Red Cell Aplasia (PRCA)	Guidance is provided in sections 4.3 Contraindications, 4.4 Special warnings and precautions for use and 4.8 Undesirable effects of the SmPC and in the patient information leaflet.	None
Thromboembolic events	Guidance is provided in sections 4.3 Contraindications, 4.4 Special warnings and precautions for use, 4.8 Undesirable effects and 5.1 Pharmacodynamic properties of the SmPC and in the patient information leaflet.	None
Hypertension / Hypertensive crisis	Guidance is provided in sections 4.3 Contraindications, 4.4 Special warnings and precautions for use and 4.8 Undesirable effects of the SmPC and in the patient information leaflet.	None
Seizure	Guidance is provided in the sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects of the SmPC and in the patient information leaflet.	None
Premature death	Guidance is provided in sections 4.4 Special warnings and precautions for use, 4.8 Undesirable effects and 5.1 Pharmacodynamic properties of the SmPC and in the patient information leaflet.	None
Hypersensitivity reactions (including anaphylactic reactions)	Guidance is provided in the sections 4.3 Contraindications and 4.8 Undesirable effects of the SmPC and in the patient information leaflet.	None
Hyperkalemia	Guidance is provided in the sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects of the SmPC and in the patient information leaflet.	None
Tumor growth potential	Guidance is provided in sections 4.4 Special warnings and precautions for use, 4.5 Interaction with other medicinal products and other forms of interaction, 5.1 Pharmacodynamic properties and 5.3 Preclinical safety data of the SmPC.	None
Congestive heart failure (CHF)	Guidance is provided in section 5.1 Pharmacodynamic properties of the SmPC.	None
Misuse	Currently available data do not support the need for risk minimization.	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Safety in lactation	Guidance is provided in the section 4.6 Fertility, Pregnancy and Lactation of the SmPC and in the patient information leaflet.	None
Safety in children	Guidance is provided in the section 4.8 Undesirable effects of the SmPC.	None

1.2 Part VI.2 Elements for a Public Summary

1.2.1 Part VI.2.1 Overview of disease epidemiology

Erythropoiesis-stimulating agents (ESAs) are important treatment options for patients with anemia as a result of chronic kidney disease (CKD), and for patients with cancer who have anemia associated with chemotherapy. CKD is characterized by a gradual loss of kidney function. As kidney function worsens, the kidney loses its ability to produce sufficient erythropoietin, leading to fewer red blood cells production (Nangaku et al 2006). More than a million patients worldwide require renal replacement therapy caused by their CKD (Schena 2000). There has been a trend towards an increasing incidence of CDK in industrialized regions for the last 20 years, due to increasing overall age and number of patients with blood pressure or diabetes mellitus (Stengel et al 2003, McClellan, 2005, Van Dijk et al 2005). Patients with cancer, particularly those receiving chemotherapy, frequently experience anemia. In the 6-month European Cancer Anemia Survey, 39.3% of cancer patients were anemic (Hb <12 g/dl) at the beginning, and more than two-thirds of these patients were found to be anemic during the survey period (Ludwig et al 2004). Chemotherapy-induced anemia primarily results from effects of the chemotherapy on the bone marrow, although some chemotherapies can directly affect the cells in the kidney (Macpherson et al 2009).

1.2.2 Part VI.2.2 Summary of treatment benefits

Anemia has a negative impact on the health of patients with CKD. It is accompanied by an increased risk of cardiovascular disease, less well-being and poorer quality of life (QoL), hospital treatment, and death (Foley et al 1998, Levin et al 1999, Ofsthun et al 2003, Perlman et al 2005). For patients with cancer, anemia has a strong impact on the QoL as a result of its symptoms such as extreme tiredness and reduced physical abilities (Cella et al 1998). Correction of anemia and maintenance of adequate hemoglobin (Hb) levels by using ESAs is therefore an important part of the management of patients in both indications. The approval study demonstrated the efficacy of i.v. HX575 in maintaining Hb levels in patients on hemodialysis (Haag-Weber et al 2009). The stability of response (measured by Hb level) and treatment dose in the long-term (over 56 weeks) has been established in this study. The similarity of HX575 and the reference product, epoetin alfa, was also shown. Other factors, most importantly change in epoetin dose, also demonstrated comparability between the drugs. The benefits of HX575 were maintained over a 56-week observation period. Subcutaneous administration of HX575 in CKD patients in the SENSE study was reported to be effective and well tolerated with a safety profile consistent with that expected for this population (Casadevall et al 2016). For cancer patients suffering from anemia caused by chemotherapy, HX575 corrected Hb levels as expected (Weigang-Köhler et al 2009). Comparable efficacy between HX575 and comparator

epoetin alfa has been demonstrated for i.v. administration. HX575 showed similar efficacy and drug behaviour as epoetin alfa. Similarly, multiple-dose s.c. HX575 and epoetin alfa demonstrated drug behaviour in healthy volunteers, and comparable Hb increases in cancer patients with anemia caused by chemotherapy. Taken together, these findings show that HX575 is a biosimilar to the reference product, and provides similar benefits as epoetin alfa by correcting and maintaining Hb levels in anemic patients.

1.2.3 Part VI.2.3 Unknowns relating to treatment benefits

Clinical experience with HX575 in patient of different ethnic origins is limited. Studies with HX575 also assessed a substantial number of elderly patients and patients of very old age with treatment benefits comparable to previous findings with ESAs. In general, the disease severity of patients in studies is representative for the target population. There are no adequate data from the use of epoetin alfa in pregnant or lactating women, or patients with genetic polymorphisms. No clinical experience with HX575 in children is available. No differences in children to adults is expected which are different to that of the reference product Erypo®/Eprex®.

1.2.4 Part VI.2.4 Summary of safety concerns

Table 1-5 Important identified risks

Risk	What is known	Preventability
Condition where the bone marrow cannot produce enough red blood cells leading to severe anemia (Pure Red Cell Aplasia (PRCA))	Up to 1 in 10,000 people using epoetin alfa can develop Symptoms of pure red cell aplasia (PRCA) PRCA means the bone marrow does not make enough red blood cells. PRCA causes sudden and severe anemia. The symptoms are: • unusual tiredness, • feeling dizzy, • breathlessness. PRCA has been very rarely reported mostly in patients with kidney disease after months to years of treatment with epoetin alfa and other products that stimulate red blood cell production. A combination of epoetin alfa with interferon and ribavirin has led to a loss of effect of epoetin alfa and development of a condition called pure red cell aplasia (PRCA), a severe form of anemia, in rare cases.	If a patient has been diagnosed with PRCA after a previous treatment with any product that stimulates red blood cell production (including Binocrit), epoetin alfa should not been used. If a patient has hepatitis C and receives interferon and ribavirin, the treatment with epoetin alfa, including Binocrit, should be discussed with the doctor. Binocrit is not approved in the management of anemia associated with hepatitis C. The doctor or nurse should be informed immediately if the patient is aware of any of these effects, or if he/she notices any other effects while he/she is receiving treatment with epoetin alfa**.** If any of the side effects gets serious, or if the patient notices any side effects not listed in the patient information leaflet, the doctor, nurse or pharmacist should be informed.

Risk	What is known	Preventability
Development of blood clots (Thromboembolic events)	Up to 1 in 10 people using epoetin alfa may develop blood clots (including deep vein thrombosis and embolism) that may require urgent treatment. The patient may have chest pain, breathlessness, and painful swelling and redness, usually in the leg as symptoms. Binocrit and other products that stimulate red cell production may increase the risk of developing blood clots in all patients. If a patient is receiving hemodialysis, blood clots (thrombosis) may form in the dialysis shunt. This is more likely if the patient has low blood pressure or if his/her fistula has complications, and blood clots may also form in the hemodialysis system.	If a patient has severe heart disease, severe disorders of the veins and arteries, recently had a heart attack or stroke, can't take medicines to thin the blood, Binocrit may not be suitable for this patient. This should be discussed with the doctor. While on Binocrit, some people need medicines to reduce the risk of blood clots. If a patient can't take medicines that prevent blood clotting, you must not have Binocrit. This risk may be higher if a patient has other risk factors for developing blood clots (for example, if he/she has had a blood clot in the past or is overweight, has diabetes, has heart disease or is off your feet for a long time because of surgery or illness). The doctor should be informed about any of these things and will help to decide if Binocrit is suitable for the patient. The doctor will maintain the patient's hemoglobin level between 10 and 12 g/dl as a high hemoglobin level may increase the risk of blood clots and death. In patients undergoing hemodialysis, the doctor may decide to increase the heparin dose during dialysis to avoid blood clot formation in the hemodialysis system or dialysis shunt.
(Severely) elevated blood pressure [severely: first blood pressure value ≥ 180 mmHg or second value ≥ 110 mmHg] (Hypertension / Hypertensive crisis)	Up to 1 in 10 people using epoetin alfa may develop increased blood pressure. Headaches, particularly sudden, stabbing migraine-like headaches, feeling confused or having fits may be signs of a sudden increase in blood pressure. This requires urgent treatment. Raised blood pressure may require treatment with some other medicines (or adjustment to any medicines you already take for high blood pressure).	Epoetin alfa should not be used if a patient has high blood pressure not properly controlled with medicines. If the patient suffers or has suffered from high blood pressure, the doctor should be informed. The doctor will monitor the blood pressure regularly while the patient is using epoetin alfa.
Seizure	Up to 1 in 100 people using epoetin alfa may develop seizures.	It is important to tell the doctor that the patient suffers from epileptic seizures or fits. He/she may still be able to use epoetin alfa, but it should be discussed with the doctor first.

Risk	What is known	Preventability
Premature death	A high hemoglobin level may increase the risk of blood clots and death in patients with kidney disease and adults on chemotherapy. In patients with chronic renal failure, repeatedly increasing the dose of epoetin alfa if a patient is not responding to treatment may increase the risk of having a problem of the heart or the blood vessels and could increase risk of myocardial infarction, stroke and death.	The doctor will maintain the hemoglobin level between 10 and 12 g/dl. The doctor will check the epoetin alfa-dose regularly, particularly if a patient with chronic renal failure does not respond properly to epoetin alfa.
Hypersensitivity reactions (including anaphylactic reactions)	Up to 1 in 10 people using epoetin alfa may develop skin rashes, which may result from an allergic reaction.	A patient should not use epoetin alfa if he/she is allergic to epoetin alfa or any of the other ingredients of this medicine.
High blood potassium (Hyperkalemia)	Up to 1 in 100 people using epoetin alfa may develop high levels of blood potassium which can cause abnormal heart rhythm (this is a very common side effect in patients on dialysis).	Electrolytes (ions which regulate the electric charge on cells and the water flow across cell membranes) should be monitored in patients with chronic insufficiency of the kidneys. If an elevated or rising potassium level is detected, then in addition to appropriate treatment of the high potassium the epoetin alfa administration should be ceased until the blood potassium level has been corrected.

Table 1-6 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Tumor growth potential	To date, no conclusive data are available about an association of tumor growth and the use of epoetin alfa.
Congestive heart failure	If a patient has chronic renal failure, and particularly if the patient does not respond properly to epoetin alfa, the doctor will check the dose of epoetin alfa because repeatedly increasing the dose of epoetin alfa if the patient is not responding to treatment may increase the risk of having a problem of the heart.
Misuse	The misuse of recombinant human erythropoietin in sports is well known. It is used as performance-enhancing drug in endurance events. Misuse can lead to serious health risks for athletes, e.g. an increased risk of heart disease, stroke, blood clot formation in the brain or lung, PRCA. Recombinant human erythropoietin, the group of drugs epoetin alfa is belonging to, has been banned as a performance-enhancing substance since the early 1990s.

Table 1-7 Missing information

Risk	What is known
Safety in lactation	It is important to tell the doctor if a patient is breast-feeding. She may still be able to use epoetin alfa, but it should be discussed with the doctor first. It is unknown whether epoetin alfa is excreted in human milk. Epoetin alfa should be used with caution in nursing women. The use of epoetin alfa is not recommended in breast-feeding women undergoing surgery and participating in a program to transfuse blood back at a later date, usually after surgery, which she stored before.
Safety in children	Experience related to a treatment of children with chronic renal failure on hemodialysis is limited. To date, no adverse reactions specific to children which differ from those undesirable effects described in the package leaflet, or any that were not consistent with the underlying disease were reported for children.

1.2.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

This medicine has no additional risk minimization measures.

1.2.6 Part VI.2.6 Planned post authorization development plan

None.