Summary of risk management plan for Abseamed/ Binocrit / Epoetin alfa Hexal/ (*INN:* epoetin alfa)

This is a summary of the risk management plan (RMP) Abseamed®/, Binocrit®/, Epoetin alfa Hexal®(epoetin alfa).The RMP details important risks of Abseamed®/ Binocrit®/ Epoetin alfa Hexal®how these risks can be minimized, and how more information will be obtained about Abseamed®/ Binocrit®/ Epoetin alfa Hexal®risks and uncertainties (missing information).

Abseamed®/ Binocrit®/ Epoetin alfa Hexal's summary of product characteristics (SmPC) and its PL give essential information to healthcare professionals and patients on how Binocrit® should be used.

This summary of the RMP for Abseamed®/ Binocrit®/ Epoetin alfa Hexal® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Abseamed®/ Binocrit®/ Epoetin alfa Hexal®'s RMP.

The medicine and what it is used for

Abseamed®/ Binocrit®/ Epoetin alfa Hexal® is indicated for the treatment of symptomatic anemia: (see SmPCs for the full indication):

- Associated with chronic renal failure (CRF) in adults and in children aged 1 to 18 years old.
- Adults receiving chemotherapy for solid tumors, malignant lymphoma or multiple myeloma and at risk of transfusion as assessed by the patient's general status (e.g. cardiovascular status, pre-existing anemia at the start of chemotherapy) for the treatment of anemia and reduction of transfusion requirements.
- Adults in a predonation program to increase the yield of autologous blood.
- In non-iron deficient adults prior to major elective orthopedic surgery, having a high perceived risk for transfusion complications to reduce exposure to allogeneic blood transfusions.
- In adults with low- or intermediate-1-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin (<200 mU/mL).

It contains epoetin alfa as the active substance and it is administered either by the subcutaneous (s.c.) or by the intravenous (i.v.) route of administration.

Further information about the evaluation of Abseamed®/ Binocrit®/ Epoetin alfa Hexal® benefits can be found in the EPAR Abseamed®, EPAR Binocrit®, EPAR Epoetin alfa Hexal®.

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000727/WC500020666.pdf

Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Abseamed®/ Binocrit®/ Epoetin alfa Hexal® together with measures to minimize such risks and the proposed studies for learning more about Abseamed®/ Binocrit®/ Epoetin alfa Hexal®'s risks, are outlined below.

- Measures to minimize the risks identified for medicinal products can be:
- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Abseamed®/ Binocrit®/ Epoetin alfa Hexal®, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Abseamed®/ Binocrit®/ Epoetin alfa Hexal® is not yet available, it is listed under 'missing information' below

List of important risks and missing information

Important risks of Abseamed®/ Binocrit®/ Epoetin alfa Hexal® are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Abseamed®/ Binocrit®/ Epoetin alfa Hexal®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	Pure Red Cell Aplasia (PRCA) Thromboembolic events Hypertension / Hypertensive crisis Seizure

List of important risks and missing information	
	Premature death
	Hypersensitivity reactions (including anaphylactic reactions)
	Hyperkalaemia
Important potential risks	Tumor growth potential
	Congestive heart failure
	Misuse
Missing information	Safety in lactation
	Safety in children

Summary of important risks

Table 2 Important identified risk: Pure Red Cell Aplasia (PRCA)

Evidence for linking the risk to the medicine	Patients with neutralizing anti-epoetin antibodies develop resistance to erythropoietin leading to severe anemia with a deep decrease in hemoglobin and in circulating reticulocytes. So far, treatment of this condition remains fully investigative and includes immunosuppressive therapy, leading to recovery of some of these patients (Macdougall et al 2015) Pre-existing non-neutralizing anti-epoetin antibodies were found to be present in 6% of subjects from oncological, nephrological and congestive heart failure clinical trials (Barger et al 2012). However, a correlation between such baseline non-neutralizing antibodies and PRCA could not been shown (Shin et al 2012). Positive non-neutralizing anti-Epo antibodies at baseline do not represent a contraindication to epoetin alfa treatment.
Risk factors and risk groups	Patients with a high tumor burden or with a high number (≥25 × 109/L) of circulating malignant cells such as patients with CLL, who may be at higher risk of especially severe cytokine release syndrome, should only be treated with extreme caution [relevant for marketing authorizations with indication CLL]. Patients with a history of pulmonary insufficiency or those with pulmonary tumor infiltration may be at greater risk of poor outcome and should be treated with increased caution.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.3, 4.4 where recommendations for monitoring hemoglobin and bone marrow examination should be consider for the diagnosis of PRCA are given, and Section 4.8. PL Section 2. Legal status: Prescription only

Additional pharmacovigilance activities	Additional pharmacovigilance activities: NIS-PASS (MEA 13.5) See Section 2.3 of this summary for an overview of the post-authorization development plan.

Table 3 Important identified risk: Thromboembolic events

Evidence for linking the risk to the medicine	An increased incidence of thrombotic vascular events (thromboses and embolism) has been observed in patients receiving ESAs, for patients with CKD, thrombotic events (incidence rate ratio, 1.25; 95% CI, 1.08 – 1.44), and dialysis vascular access thrombosis (incidence rate ratio 1.17; 95% CI, 1.07 – 1.29) increased (Koulouridis et al 2013). In cancer patients the receipt of ESA increased the risk for thrombotic events (odds ratio 1.56) (Khorana 2013).
Risk factors and risk groups	Obese patients, patients with cancer and patients with a history of thrombotic vascular events are at increased risk. Shunt thromboses have occurred in hemodialysis patients, especially in those who have a tendency to hypotension or whose arteriovenous fistulae exhibit complications (e.g. stenoses, aneurysms etc.). Patients with major surgery are at increased risk, especially in those with underlying cardiovascular disease.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.3, 4.4 where recommendations for monitoring hemoglobin in patients receiving epoetin alfa and the administration of antithrombotic prophylaxis in patients scheduled for major elective orthopedic surgery are given , and Sections 4.8 and 5.1. PL Section 3. Legal status: Prescription only
Additional pharmacovigilance activities	Additional pharmacovigilance activities: TRIGONS study, study MEA 18; HX575-502, pharmacoepidemiological study, MEA 18 is related to LEG027/028 See Section 2.3 of this summary for an overview of the post-authorization development plan.

Table 4	**Important identified risk: Hypertension / hypertensive crisis**
Evidence for linking the risk to the medicine	There is compelling evidence that treatment by ESA generate hypertension (Krapf and Hulter 2009), and some authors have shown that hypertension of sufficient severity to require hospital admission occurred in over 10% of Epo-treated patients, and at a rate nearly three times that of placebo. The finding of a fivefold elevation of hypertensive encephalopathy is even more noteworthy. The report of Abraham et al is unique in that it analyzed a subset with no exposure to BP medication and found that Epo-treated subjects had large and significant increases in BP relative to subjects on placebo (DBP + 6 and SBP + 13 mmHg, net of placebo, both $P < 0.05$). These data are likely the best index of Epo side effects on BP in any population reported to date. There is an apparent tendency for the magnitude of the BP effect of Epo to be greater in patients receiving hemodialysis than in those who are predialysis or receiving peritoneal dialysis.
Risk factors and risk groups	Patients with a history of hypertension might be at a higher risk to develop hypertensive complications (Brunkhorst et al 1991).
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.3, 4.4 where recommendations for monitoring blood pressure and if blood pressure cannot be controlled, epoetin alfa treatment should be discontinued are given , and Section 4.8 PL Section 3. Legal status: Prescription only

Table 5	**Important identified risk: Seizure**
Evidence for linking the risk to the medicine	Most of the epidemiological studies of epilepsy find an incidence rate of 20-70/100,000 per year (range 11-134/100,000) (Halatchev 2000). Isolated cases have been reported so far. In all patients confounding history was present. (SmPC Binocrit/Abseamed/Epoetin alfa HEXAL, 2018)
Risk factors and risk groups	Patients with epilepsy, history of seizures, or medical conditions associated with a predisposition to seizure activity such as CNS infections and brain metastases.
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4

	where recommendations to use epoetin alfa with caution in patients with epilepsy, history of seizures, or medical conditions associated with a predisposition to seizure activity such as CNS infections and brain metastases are given , and Section 4.8 PL Section 2 where recommendations are given to patients to inform their doctors if they suffer/have suffered from epileptic seizures or fits. Legal status: Prescription only

Table 6 Important identified risk: Premature death

Evidence for linking the risk to the medicine	Increased risk of death in trials in case the hemoglobin target level was at least 12g/dL (7.5 mmol/L).
Risk factors and risk groups	Venous and arterial thrombosis listed for epoetin may lead to a fatal outcome. Shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to achieve a hemoglobin concentration range of 12 to 14 g/dL (7.5 to 8.7 mmol/L) Increased risk of death when administered to achieve a hemoglobin concentration level of 12 g/dL (7.5 mmol/L) in patients with active malignant disease receiving neither chemotherapy nor radiation therapy.
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4 where recommendations to closely monitor high levels of hemoglobin are given due to a potential increased risk of thromboembolic events and fatal outcomes, and Sections 4.8 and 5.1. PL Section 2. Legal status: Prescription only

Table 7 Important identified risk: Hypersensitivity reactions (including anaphylactic reactions)

Evidence for linking the risk to the medicine	Hypersensitivity to the active ingredient is a plausible mechanism. Incidence appears slightly higher in patients with cancer, however a smaller sample size than 2 other groups, severity appears mostly mild in all groups, and recovery is reported in most patients; however rare fatal cases are reported in the larger groups, i.e. patients with CKD.
Risk factors and risk groups	Patients with known hypersensitivity to epoetin are at increased risk. Otherwise, no risk groups or risk factors are known.

Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.3 and 4.8 Legal status: Prescription only

Table 8 Important identified risk: Hyperkalemia

Evidence for linking the risk to the medicine	Mechanism is unknown. Common in patients with CKD (Kovesdy 2014); Isolated cases have been reported so far (SmPC Binocrit/Abseamed/Epoetin alfa HEXAL, 2018). Symptoms are mostly unspecific. However severe hyperkalemia can induce potential fatal cardiac arrhythmia.
Risk factors and risk groups	Patients with CKD are at increased risk due to the effects of kidney dysfunction on potassium homeostasis.
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4 where recommendations to monitor serum electrolytes should be monitored in chronic renal failure patients and cease epoetin alfa administration until the serum potassium level has been corrected and Section 4.8. PL Section 3. Legal status: Prescription only

Table 9 Important potential risk: Tumor growth potential

Evidence for linking the risk to the medicine	Erythropoietin receptors may be expressed on the surface of a variety of tumour cells. As with all growth factors, there is a concern that epoetins could stimulate the growth of tumours. Conflicting reports in the literature, based on in vitro findings from human tumour samples, suggest erythropoietins may play a role as tumour proliferators. This is of uncertain significance in the clinical situation
Risk factors and risk groups	Information not available.
Risk minimization measures	Routine risk minimization measures: SmPC Sections 4.4, 4.5, 5.1 and 5.3 PL Section 2 Legal status: Prescription only
Additional pharmacovigilance activities	Additional pharmacovigilance activities: TRIGONS study (MEA 18; HX575-502) See Section 2.3 of this summary for an overview of the post-authorization development plan.

Table 10 Important potential risk: Congestive heart failure (CHF)

Evidence for linking the risk to the medicine	The CHOIR study (Singh et al 2006) showed increased risk of Congestive Heart Failure in subjects included in the high target hemoglobin group (13.5 g/dL vs. 11.3 g/dL).
Risk factors and risk groups	Most important conditions/diseases which lead to CHF are: myocardial infarction and hypertension (Mann and Chakinala 2012). In the context of anemia, low hemoglobin as well as normalized hemoglobin may both trigger worsening in patients with pre-existing condition, through low myocardial oxygen perfusion or hyperviscosity respectively. In addition, hypertension worsening/new onset under epoetin may also trigger CHF.
Risk minimization measures	Routine risk minimization measures: SmPC Section 5.1 PL Section 2. Legal status: Prescription only

Table 11 Important potential risk: Misuse

Evidence for linking the risk to the medicine	Recombinant human erythropoietin is used as performance-enhancing drug in endurance events. In addition to increased oxygen supply, epoetin also increases the body's capacity to buffer lactic acid (World Anti-Doping Code 2006).
Risk factors and risk groups	The misuse of recombinant human erythropoietin in sports athletes is well known
Risk minimization measures	Routine risk minimization measures: SmPC section: None PL section: None. Legal status: Prescription only

Table 12 Missing information: Safety in lactation

Risk minimization measures	Routine risk minimization measures: SmPC Section 4.6 where recommendation is given to physicians discontinue/abstain from therapy with epoetin alfa taking into account the benefit of breast-feeding for the child and the benefit of epoetin alfa therapy for the woman. PL Section 2 where recommendation is given to patients to tell their doctors if they are pregnant/planning to be or if they are breast-feeding. Legal status: Prescription only

Table 13 Missing information: Safety in children

Risk minimization measures	Routine risk minimization measures: SmPC Section 4.8 PL section: None Legal status: Prescription only

Post-authorization development plan

Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Abseamed®/ Binocrit®/ Epoetin alfa Hexal®.

Other studies in post-authorization development plan

Table 14 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
NIS-PASS (MEA 13.5)	Non-interventional Post-Approval Safety Study, reporting the safety of s.c. HX575 treatment in 2500 CKD patients over 24 months.
TRIGONS study MEA 18; HX575-502 pharmacoepidemiological study MEA 18 is related to LEG027/028.	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.