EU Risk Management Plan (RMP) for Epoetin Alfa (Abseamed®, Binocrit®, Epoetin alfa Hexal®) 16.8 µg/mL, 84 µg/mL and 336 µg/mL Solution for Injection

RMP version to be assessed as part of this application:

RMP Version number: 19.1

Data lock point for this RMP: 30-Apr-2024

Date of final sign off: 03-Jun-2024

Rationale for submitting an updated RMP: The RMP has been updated to address the comments received from PRAC dated 29 April 2024 under procedure number EMEA/H/C/WS2615.

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v19.0
Part I	Updated sub-heading of Table i.e., number of medicinal products as "3".
Part II	• Module SV: Exposure data has been updated till 30-April-2024. • Module SVII and Module SVIII: Removal of all the below mentioned safety concerns. – Pure Red Cell Aplasia (PRCA). – Disease progression. – Survival impact.
Part III	• Part III.1 have been updated with routine PV activities are in place. • Part III.3 has been updated to "not applicable".
Part V	• Part V.1 has been updated with statement "Routine risk minimization measures are in place.". • Part V.2 and Part V.3 have been updated to "Not applicable".
Part VI	• Aligned with the changes made in the RMP. Also, update has been done for Part VI.II.C.2 by adding statement "There are no studies required for Abseamed®/ Binocrit®/ Epoetin alfa Hexal®. Part VI.II has been updated by removing following statements: – In the case of Abseamed®/ Binocrit®/ Epoetin alfa Hexal®, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below. – 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.
Part VII	• Annex 7 - Included the reference of PRAC assessment report. • Annex 8 - Summary of changes to the RMP over time.

Other RMP versions under evaluation: None

Details of the currently approved RMP:

Version number: 18.1

Approved with procedure: EMEA/H/C/WS2013

Date of approval (opinion date): 08-Jul-2021

EU QPPV name: Juergen Maares

EU QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s EU QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

Acronym	Definition
ADR	Adverse Drug Reaction
AE	Adverse Events
CI	Confidence Interval
CKD	Chronic Kidney Disease
CNS	Central Nervous System
CRF	Chronic Renal Failure
CSF	Colony-stimulating factor
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agent
EU	European Union
GVP	Guideline on Good Pharmacovigilance Practices
Hb	Hemoglobin
IU	International units
i.v.	Intravenous
MDS	Myelodysplastic Syndromes
MedDRA	Medical Dictionary for Regulatory Activities
PFS	Pre-Filled Syringe
PL	Package Leaflet
PRCA	Pure Red Cell Aplasia
PSUR	Periodic Safety Update Report
PT	Preferred Term

Acronym	**Definition**
QPPV	Qualified Person for Pharmacovigilance
RBC	Red Blood Cell
RMP	Risk Management Plan
SAE	Serious Adverse Event
s.c.	Subcutaneous
SCARs	Severe Cutaneous Adverse Reactions
SmPC	Summary of Product Characteristics
SOC	System Organ Class

Part I: Product(s) Overview

Table 1 Part I.1 – Product Overview

Active substance(s) (INN or common name)	Epoetin alfa
Pharmacotherapeutic group(s) (ATC Code)	Anti-anaemic preparations, other anti-anaemic preparations (B03XA01)
Marketing Authorization Holder	Sandoz GmbH
Medicinal products to which this RMP refers	3
Invented name(s) in the European Economic Area (EEA)	Abseamed®, Binocrit®, Epoetin alfa Hexal®
Marketing authorisation procedure	Centralized.
Brief description of the product	**Chemical class**: Erythropoietin (EPO) is a glycoprotein hormone produced primarily by the kidney in response to hypoxia that primarily stimulates red blood cell (RBC) production. Recombinant human EPO (epoetin alfa) is expressed in Chinese hamster ovary cells.
	Summary of mode of action: EPO is involved in all phases of erythroid development and has its principal effect at the level of erythroid precursors. After EPO binds to its cell surface receptor, it activates signal transduction pathways that interfere with apoptosis and stimulates erythroid cell proliferation.
	Important information about its composition: Produced in Chinese Hamster Ovary (CHO) cells by recombinant deoxyribonucleic acid (DNA) technology. This medicinal product contains less than 1 mmol sodium (23 mg) per dose, which is essentially "sodium free".
Hyperlink to the Product Information	[Current SmPC in Module 1.3.1]
Indication(s) in the EEA	**Current**: Epoetin alfa is indicated for the treatment of symptomatic anemia associated with chronic renal failure (CRF): – in adults and children aged 1 to 18 years on hemodialysis and adult patients on peritoneal dialysis. – in adults with renal insufficiency not yet undergoing dialysis for the treatment of severe anemia of renal origin accompanied by clinical symptoms in patients. Epoetin alfa is indicated in 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. Epoetin alfa is indicated in adults in a predonation program to increase the yield of

	autologous blood. Treatment should only be given to patients with moderate anemia (Hemoglobin (Hb) concentration range between 10–13 g/dL or (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). Epoetin alfa is indicated for 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. Use should be restricted to patients with moderate anemia (e g., Hb in concentration range between 10-13 g/dL or 6.2-8.1 mmol/L) who do not have an autologous predonation program available and with expected moderate blood loss (900 to 1,800 mL). Epoetin alfa is indicated for the treatment of symptomatic anemia (hemoglobin concentration of ≤10 g/dL) in adults with low- or intermediate- 1-risk primary MDS who have low serum erythropoietin (<200 mU/mL).
Dosage in the EEA	**Current**: *Treatment of symptomatic anemia in adult chronic renal failure patients:* Anemia symptoms and sequelae may vary with age, gender, and co-morbid medical conditions; a physician's evaluation of the individual patient's clinical course and condition is necessary. The recommended desired hemoglobin concentration range is between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L). Epoetin alfa should be administered in order to increase hemoglobin to not greater than 12 g/dL (7.5 mmol/L). A rise in hemoglobin of greater than 2 g/dL (1.25 mmol/L) over a four week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided. Due to intra-patient variability, occasional individual hemoglobin values for a patient above and below the desired hemoglobin concentration range may be observed. Hemoglobin variability should be addressed through dose management, with consideration for the hemoglobin concentration range of 10 g/dL (6.2 mmol/L) to 12 g/dL (7.5 mmol/L). A sustained hemoglobin level of greater than 12 g/dL (7.5 mmol/L) should be avoided. If the hemoglobin is rising by more than 2 g/dL (1.25 mmol/L) per month, or if the sustained hemoglobin exceeds 12 g/dL (7.5 mmol/L) reduce the epoetin alfa dose by 25%. If the hemoglobin exceeds 13 g/dL (8.1 mmol/L), discontinue therapy until it falls below 12 g/dL (7.5 mmol/L). and then reinstitute epoetin alfa therapy at a dose 25% below the previous dose. Patients should be monitored closely to ensure that the lowest approved effective dose of epoetin alfa is used to provide adequate control of anemia and of the symptoms of anemia whilst maintaining a hemoglobin concentration below or at 12 g/dL (7.5 mmol/L). Caution should be exercised with escalation of epoetin alfa doses in patients with chronic renal failure. In patients with a poor hemoglobin response to epoetin alfa, alternative explanations for the poor response should be considered.

	Treatment with epoetin alfa is divided into two stages – correction and maintenance phase. *Adult hemodialysis patients:* In patients on hemodialysis where intravenous access is readily available, administration by the intravenous route is preferable. *Correction phase:* The starting dose is 50 IU (international units)/kg, 3 times per week. If necessary, increase or decrease the dose by 25 IU/kg (3 times per week) until the desired hemoglobin concentration range between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/Ll) is achieved (this should be done in steps of at least four weeks). *Maintenance phase:* During the maintenance phase, epoetin alfa can be administered either 3 times per week, and in the case of subcutaneous administration, once weekly or once every 2 weeks. Appropriate adjustment of dose and dose intervals should be made in order to maintain hemoglobin values within the desired level: hemoglobin between 10 g/dL and 12 g/dL (6.2 to 7.5 mmol/L). Patients with very low initial haemoglobin (< 6 g/dL or < 3.75 mmol/L) may require higher maintenance doses than patients whose initial anaemia is less severe (> 8 g/dL or > 5 mmol/L). *Adult patients with renal insufficiency not yet undergoing dialysis:* Where intravenous access is not readily available Epoetin Alfa may be administered subcutaneously. *Correction phase:* Starting dose of 50 IU/kg, 3 times per week, followed if necessary by a dosage increase with 25 IU/kg increments (3 times per week) until the desired goal is achieved (this should be done in steps of at least four weeks). *Maintenance phase:* During the maintenance phase, Epoetin Alfa can be administered either 3 times per week, and in the case of subcutaneous administration, once weekly or once every 2 weeks. Appropriate adjustment of dose and dose intervals should be made in order to maintain haemoglobin values at the desired level: haemoglobin between 10 g/dL and 12 g/dL (6.2 to 7.5 mmol/L). Extending dose intervals may require an increase in dose. The maximum dosage should not exceed 150 IU/kg, 3 times per week, 240 IU/kg

	(up to a maximum of 20,000 IU) once weekly, or 480 IU/kg (up to a maximum of 40,000 IU) once every 2 weeks. *Adult peritoneal dialysis patients:* Where intravenous access is not readily available epoetin alfa may be administered subcutaneously. *Correction phase:* The starting dose is 50 IU/kg, 2 times per week. *Maintenance phase:* The recommended maintenance dose is between 25 IU/kg and 50 IU/kg, 2 times per week in 2 equal injections. Appropriate adjustment of the dose should be made in order to maintain hemoglobin values at the desired level between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L). *Treatment of adult patients with chemotherapy-induced anemia:* Anemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary. Epoetin alfa should be administered to patients with anemia (e.g. hemoglobin concentration ≤ 10 g/dL (6.2 mmol/L)). The initial dose is 150 IU/kg subcutaneously, 3 times per week. Alternatively, epoetin alfa can be administered at an initial dose of 450 IU/kg subcutaneously once weekly. Appropriate adjustment of the dose should be made in order to maintain hemoglobin concentrations within the desired concentration range between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L). Due to intra-patient variability, occasional individual hemoglobin concentrations for a patient above and below the desired hemoglobin concentration range may be observed. Hemoglobin variability should be addressed through dose management, with consideration for the desired hemoglobin concentration range between 10 g/dL (6.2 mmol/L) to 12 g/dL (7.5 mmol/L). A sustained hemoglobin concentration of greater than 12 g/dL (7.5 mmol/L) should be avoided; guidance for appropriate dose adjustment for when hemoglobin concentrations exceed 12 g/dL (7.5 mmol/L) is described below. - If the hemoglobin concentration has increased by at least 1 g/dL(0.62 mmol/L) or the reticulocyte count has increased ≥ 40,000 cells/µL above baseline after 4 weeks of treatment, the dose should remain at 150 IU/kg 3 times per week or 450 IU/kg once weekly. - If the hemoglobin concentration increase is < 1 g/dL (< 0.62 mmol/L) and the reticulocyte count has increased < 40,000 cells/µL above baseline, increase the dose to 300 IU/kg 3 times per week. If after an additional 4 weeks of therapy at

300 IU/kg 3 times per week, the hemoglobin concentration has increased ≥ 1 g/dL (≥ 0.62 mmol/L) or the reticulocyte count has increased ≥ 40,000 cells/µL, the dose should remain at 300 IU/kg 3 times per week.

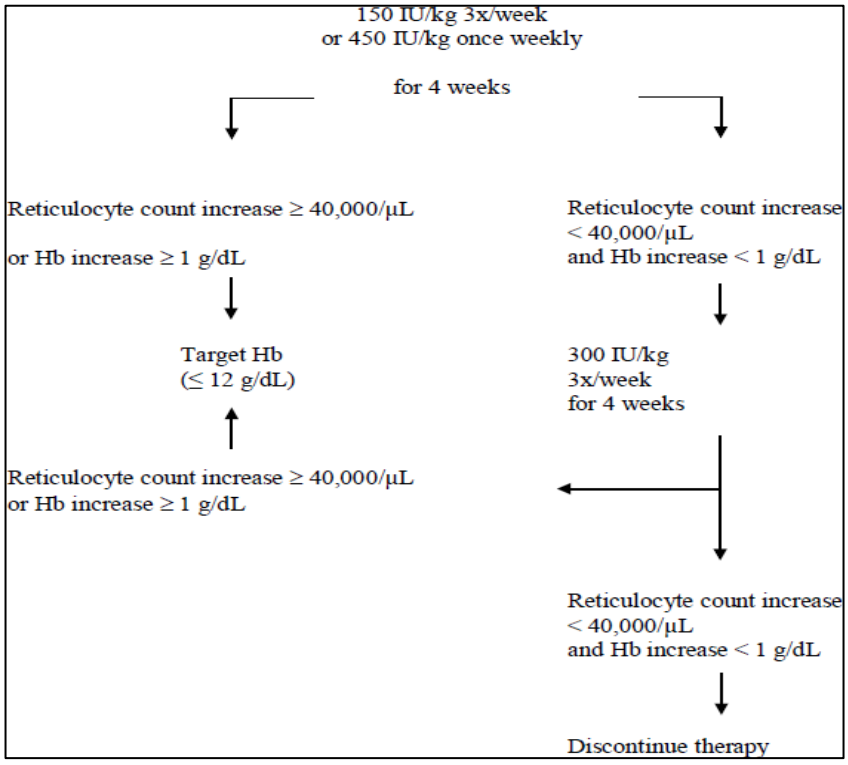
- If the hemoglobin concentration has increased < 1 g/dL (< 0.62 mmol/L) and the reticulocyte count has increased < 40,000 cells/µL above baseline, response is unlikely and treatment should be discontinued.

Dose adjustment to maintain hemoglobin concentrations between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L)

If the hemoglobin concentration is increasing by more than 2 g/dL (1.25 mmol/L) per month, or if the hemoglobin concentration level exceeds 12 g/dL (7.5 mmol/L), reduce the epoetin alfa dose by about 25 to 50%.

If the hemoglobin concentration level exceeds 13 g/dL (8.1 mmol/L), discontinue therapy until it falls below 12 g/dL (7.5 mmol/L) and then reinitiate epoetin alfa therapy at a dose 25% below the previous dose.

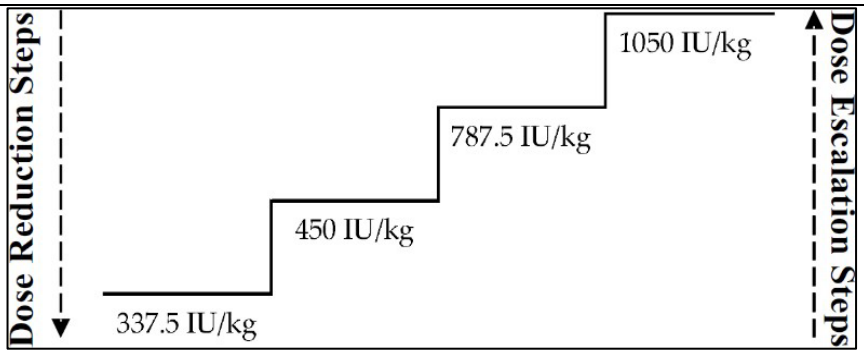
The recommended dosing regimen is described in the following diagram:



Patients should be monitored closely to ensure that the lowest approved dose of erythropoiesis-stimulating agent (ESA) is used to provide adequate control of the symptoms of anemia.

Epoetin alfa therapy should continue until one month after the end of chemotherapy.

	Treatment of adult surgery patients in an autologous predonation programme Mildly anemic patients (hematocrit of 33 to 39 %) requiring predeposit of ≥4 units of blood should be treated with epoetin alfa 600 IU/kg intravenously, 2 times per week for 3 weeks prior to surgery. Epoetin alfa should be administered after the completion of the blood donation procedure. *Treatment of adult patients scheduled for major elective orthopedic surgery* The recommended dose is epoetin alfa 600 IU/kg, administered subcutaneously weekly for three weeks (days -21, -14 and -7) prior to surgery and on the day of surgery (day 0). In cases where there is a medical need to shorten the lead time before surgery to less than three weeks, epoetin alfa 300 IU/kg should be administered subcutaneously daily for 10 consecutive days prior to surgery, on the day of surgery and for four days immediately thereafter. If the hemoglobin level reaches 15 g/dL (9.38 mmol/L), or higher, during the preoperative period, administration of epoetin alfa should be stopped and further dosages should not be administered. *Treatment of adult patients with low- or intermediate-1-risk MDS* Epoetin alfa should be administered to patients with symptomatic anemia (e.g., hemoglobin concentration ≤ 10 g/dL (6.2 mmol/L)). The recommended starting dose is epoetin alfa 450 IU/kg (maximum total dose is 40,000 IU) administered subcutaneously once every week, with not less than 5 days between doses. Appropriate dose adjustments should be made to maintain hemoglobin concentrations within the target range of 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L). It is recommended that initial erythroid response be assessed 8 to 12 weeks following initiation of treatment. Dose increases and decreases should be done one dosing step at a time (see diagram below). A hemoglobin concentration of greater than 12 g/dL (7.5 mmol/L) should be avoided. Dose increase: Dose should not be increased over the maximum of 1050 IU/kg (total dose 80,000 IU) per week. If the patient loses response or hemoglobin concentration drops by ≥ 1 g/dL upon dose reduction the dose should be increased by one dosing step. A minimum of 4 weeks should elapse between dose increases. Dose hold and decrease: Epoetin alfa should be withheld when the hemoglobin concentration exceeds 12 g/dL (7.5 mmol/L). Once the hemoglobin level is < 11 g/dL the dose can be restarted on the same dosing step or one dosing step down based on physician judgement. Decreasing the dose by one dosing step should be considered if there is a rapid increase in hemoglobin (> 2 g/dL over 4 weeks).



Anemia symptoms and sequelae may vary with age, gender, and co-morbid medical conditions; a physician's evaluation of the individual patient's clinical course and condition is necessary.

Pediatric population:

Treatment of symptomatic anemia in chronic renal failure patients on hemodialysis:

Anemia symptoms and sequelae may vary with age, gender, and co-morbid medical conditions; a physician's evaluation of the individual patient's clinical course and condition is necessary.

In pediatric patients the recommended hemoglobin concentration range is between 9.5 g/dL to 11 g/dL (5.9 to 6.8 mmol/L). Epoetin alfa should be administered in order to increase hemoglobin to not greater than 11 g/dL (6.8 mmol/L). A rise in hemoglobin of greater than 2 g/dL (1.25 mmol/L) over a four week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.

Patients should be monitored closely to ensure that the lowest approved dose of epoetin alfa is used to provide adequate control of anemia and of the symptoms of anemia.

Treatment with epoetin alfa is divided into two stages – correction and maintenance phase.

In pediatric patients on hemodialysis where intravenous access is readily available, administration by the intravenous route is preferable.

Correction phase:

The starting dose is 50 IU/kg intravenously, 3 times per week.

If necessary, increase or decrease the dose by 25 IU/kg (3 times per week) until the desired hemoglobin concentration range of between 9.5 g/dL to 11 g/dL (5.9 to 6.8 mmol/L) is achieved (this should be done in steps of at least four weeks).

Maintenance phase:

Appropriate adjustment of the dose should be made in order to maintain hemoglobin levels within the desired concentration range between 9.5 g/dL to 11 g/dL (5.9 to 6.8 mmol/L).

Generally, children under 30 kg require higher maintenance doses than children over

	30 kg and adults. Pediatric patients with very low initial hemoglobin (< 6.8 g/dL or < 4.25 mmol/L) may require higher maintenance doses than patients whose initial hemoglobin is higher (> 6.8 g/dL or > 4.25 mmol/L). *Anemia in chronic renal failure patients before initiation of dialysis or on peritoneal dialysis:* The safety and efficacy of epoetin alfa in chronic renal failure patients with anemia before initiation of dialysis or on peritoneal dialysis have not been established. Currently available data for subcutaneous use of epoetin alfa in these populations are available but no recommendation on posology can be made. *Treatment of pediatric patients with chemotherapy-induced anemia:* The safety and efficacy of epoetin alfa in pediatric patients receiving chemotherapy have not been established. *Treatment of pediatric surgery patients in an autologous predonation programme:* The safety and efficacy of epoetin alfa in pediatrics have not been established. No data are available. *Treatment of pediatric patients scheduled for major elective orthopedic surgery:* The safety and efficacy of epoetin alfa in pediatrics have not been established. No data are available. *Method of administration:* Precautions to be taken before handling or administering the medicinal product. Before use, leave the epoetin alfa syringe to stand until it reaches room temperature. This usually takes between 15 and 30 minutes. As with any other injectable product, check that there are no particles in the solution or change in color. Epoetin alfa is a sterile but unpreserved product and is for single use only. Administer the amount required. *Treatment of symptomatic anemia in adult chronic renal failure patients:* In patients with chronic renal failure where intravenous access is routinely available (hemodialysis patients) administration of epoetin alfa by the intravenous route is preferable. Where intravenous access is not readily available (patients not yet undergoing dialysis and peritoneal dialysis patients) epoetin alfa may be administered as a subcutaneous injection. *Treatment of adult patients with chemotherapy-induced anemia:* Epoetin alfa should be administered as a subcutaneous injection. *Treatment of adult surgery patients in an autologous predonation programme:* Epoetin alfa should be administered by the intravenous route.

	Treatment of adult patients scheduled for major elective orthopedic surgery: Epoetin alfa should be administered as a subcutaneous injection. *Treatment of adult patients with low- or intermediate-1-risk MDS:* Epoetin alfa should be administered as a subcutaneous injection. *Treatment of symptomatic anemia in pediatric chronic renal failure patients on hemodialysis:* In pediatric patients with chronic renal failure where intravenous access is routinely available (hemodialysis patients) administration of epoetin alfa by the intravenous route is preferable. *Intravenous administration:* Administer over at least one to five minutes, depending on the total dose. In hemodialysed patients, a bolus injection may be given during the dialysis session through a suitable venous port in the dialysis line. Alternatively, the injection can be given at the end of the dialysis session via the fistula needle tubing, followed by 10 mL of isotonic saline to rinse the tubing and ensure satisfactory injection of the product into the circulation. A slower administration is preferable in patients who react to the treatment with "flu-like" symptoms. Do not administer epoetin alfa by intravenous infusion or in conjunction with other medicinal product solutions. *Subcutaneous administration:* A maximum volume of 1 mL at one injection site should generally not be exceeded. In case of larger volumes, more than one site should be chosen for the injection. The injections should be given in the limbs or the anterior abdominal wall. In those situations, in which the physician determines that a patient or caregiver can safely and effectively administer epoetin alfa subcutaneously themselves, instruction as to the proper dosage and administration should be provided. *Graduation rings:* The syringe contains graduation rings to provide for the administration of a part of the dose. However, the product is for single use only. Only one dose of epoetin alfa from each syringe should be taken.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	**Current**: Binocrit/Abseamed/Epoetin alfa Hexal 1,000 IU/0.5 mL solution for injection in a pre-filled syringe Each mL of solution contains 2,000 IU of epoetin alfa corresponding to 16.8 micrograms per mL. A pre-filled syringe of 0.5 mL contains 1,000 IU corresponding to 8.4 micrograms epoetin alfa.

	Binocrit/Abseamed/Epoetin alfa Hexal 2,000 IU/1 mL solution for injection in a pre-filled syringe Each mL of solution contains 2,000 IU of epoetin alfa corresponding to 16.8 micrograms per mL. A pre-filled syringe of 1 mL contains 2,000 international units (IU) corresponding to 16.8 micrograms epoetin alfa. Binocrit/Abseamed/Epoetin alfa Hexal 3,000 IU/0.3 mL solution for injection in a pre-filled syringe Each mL of solution contains 10,000 IU of epoetin alfa corresponding to 84.0 micrograms per mL A pre-filled syringe of 0.3 mL contains 3,000 international units (IU) corresponding to 25.2 micrograms epoetin alfa. Binocrit/Abseamed/Epoetin alfa Hexal 4,000 IU/0.4 mL solution for injection in a pre-filled syringe Each mL of solution contains 10,000 IU of epoetin alfa corresponding to 84.0 micrograms per mL A pre-filled syringe of 0.4 mL contains 4,000 international units (IU) corresponding to 33.6 micrograms epoetin alfa. Binocrit/Abseamed/Epoetin alfa Hexal 5,000 IU/0.5 mL solution for injection in a pre-filled syringe Each mL of solution contains 10,000 IU of epoetin alfa corresponding to 84.0 micrograms per mL. A pre-filled syringe of 0.5 mL contains 5,000 international units (IU) corresponding to 42.0 micrograms epoetin alfa. Binocrit/Abseamed/Epoetin alfa Hexal 6,000 IU/0.6 mL solution for injection in a pre-filled syringe Each mL of solution contains 10,000 IU of epoetin alfa corresponding to 84.0 micrograms per mL. A pre-filled syringe of 0.6 mL contains 6,000 international units (IU) corresponding to 50.4 micrograms epoetin alfa. Binocrit/Abseamed/Epoetin alfa Hexal 7,000 IU/0.7 mL solution for injection in a pre-filled syringe Each mL of solution contains 10,000 IU of epoetin alfa corresponding to 84.0 micrograms per mL. A pre-filled syringe of 0.7 mL contains 7,000 international units (IU) corresponding to 58.8 micrograms epoetin alfa. Binocrit/Abseamed/Epoetin alfa Hexal 8,000 IU/0.8 mL solution for injection in a pre-filled syringe Each mL of solution contains 10,000 IU of epoetin alfa corresponding to 84.0 micrograms per mL. A pre-filled syringe of 0.8 mL contains 8,000 international units (IU) corresponding

	to 67.2 micrograms epoetin alfa. Binocrit/Abseamed/Epoetin alfa Hexal 9,000 IU/0.9 mL solution for injection in a pre-filled syringe Each mL of solution contains 10,000 IU of epoetin alfa corresponding to 84.0 micrograms per mL. A pre-filled syringe of 0.9 mL contains 9,000 international units (IU) corresponding to 75.6 micrograms epoetin alfa. Binocrit/Abseamed/Epoetin alfa Hexal 10,000 IU/1 mL solution for injection in a pre-filled syringe Each mL of solution contains 10,000 IU of epoetin alfa corresponding to 84.0 micrograms per mL. A pre-filled syringe of 1 mL contains 10,000 international units (IU) corresponding to 84.0 micrograms epoetin alfa. Binocrit/Abseamed/Epoetin alfa Hexal 20,000 IU/0.5 mL solution for injection in a pre-filled syringe Each mL of solution contains 40,000 IU of epoetin alfa corresponding to 336.0 micrograms per mL. A pre-filled syringe of 0.5 mL contains 20,000 international units (IU) corresponding to 168.0 micrograms epoetin alfa. Binocrit/Abseamed/Epoetin alfa Hexal 30,000 IU/0.75 mL solution for injection in a pre-filled syringe Each mL of solution contains 40,000 IU of epoetin alfa corresponding to 336.0 micrograms per mL. A pre-filled syringe of 0.75 mL contains 30,000 international units (IU) corresponding to 252.0 micrograms epoetin alfa. Binocrit/Abseamed/Epoetin alfa Hexal 40,000 IU/1 mL solution for injection in a pre-filled syringe Each mL of solution contains 40,000 IU of epoetin alfa corresponding to 336.0 micrograms per mL. A pre-filled syringe of 1 mL contains 40,000 international units (IU) corresponding to 336.0 micrograms epoetin alfa.
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No.

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable since Epoetin Alfa is a biosimilar product.

Part II: Module SII - Non-clinical part of the safety specification

The clinical use of epoetin alfa is well established. There are no safety concerns of HX575 that have not been adequately addressed by clinical data or which are of unknown significance.

The assessment of non-clinical safety concerns for HX575 is based on a 13-week multiple dose toxicity study and studies on local tolerability performed with HX575. It is extended by publicly available non-clinical safety data on the reference drug, Erypo®/Eprex®. Bridging to these originator data was achieved through demonstration of similar physico-chemical and non-clinical as well as clinical pharmacokinetic/pharmacodynamic (PK/PD) characteristics.

In single dose toxicity studies conducted with the reference product (Eprex®), in all tested species (mouse, rat, monkey, and dog), acute toxicity was confined to exaggerated pharmacological effect of the drug, i.e., stimulation of erythropoiesis. The studies did not demonstrate any lethality or overt signs of toxicity when given by the intravenous, intramuscular and oral route, and up to very high doses, such as 20,000 IU/kg, which corresponds to 40 times the highest anticipated human dose.

In some repeated dose toxicological studies in dogs and rats, but not in monkeys, epoetin alfa therapy was associated with subclinical bone marrow fibrosis. Following a treatment free recovery phase, fibrosis was less than observed at the end of treatment. Bone marrow fibrosis is a known complication of chronic renal failure in humans and may be related to secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis was not increased in a prospective bone marrow histology study of hemodialysis patients who were treated with epoetin alfa for a median of 15.8 months compared to a matched control group of dialysis patients who had not been treated with any ESA over a median 6 years of hemodialysis (Tulliez et al 1989)

Further alterations to normal physiology observed in all species can be attributed to direct and adaptive responses of the organism to the massive erythropoietic impulse through the epoetin alfa treatment, especially in the high-dose groups. These responses were sometimes accompanied by severe congestion of inner organs, in particular in spleen, liver and kidneys.

In animal studies, epoetin alfa has been shown to decrease fetal body weight, delay ossification and increase fetal mortality when given in weekly doses of approximately 20 times the recommended human weekly dose. These changes are interpreted as being secondary to decreased maternal body weight gain.

Epoetin alfa did not show any changes in bacterial and mammalian cell culture mutagenicity tests and an in vivo micronucleus test in mice.

Long-term carcinogenicity studies have not been carried out. There are conflicting reports in the literature regarding whether erythropoietins may play a major role as tumor proliferators. These reports are based on *in vitro* findings from human tumor samples but are of uncertain significance in a clinical situation.

Local tolerability of HX575 following subcutaneous application of epoetin alfa was at least as good as following intravenous administration.

Table 2 Key safety findings from non-clinical studies and relevance to human usage:

Key Safety Findings (From non-clinical studies)	Relevance to human usage
Single and repeated dose toxicity studies	
	No safety concern apparent.
Genotoxicity and carcinogenicity	
Genotoxicity: no own studies were performed by Sandoz; Epoetin alfa is not considered to have mutagenic potential (SmPC Eprex®). Carcinogenicity: no own studies were performed by Sandoz.	No safety concern apparent.
Carcinogenicity: no own studies were performed by Sandoz.	The impact of epoetin on survival of cancer patients is unclear (SmPC Eprex®); no risk beyond that of the reference drug is anticipated.
Reproductive toxicology	
Reproductive toxicology: no own studies were performed by Sandoz.	Changes seen with the originator drug are interpreted as being secondary to decreased maternal body weight gain, and the significance to humans is unknown given therapeutic dose levels (SmPC Eprex®); no risk beyond that of the reference drug is anticipated.
Local tolerance	
Local tolerance: 3 different studies in rabbits with HX575: the doses administered i.v., s.c. and intra- arterial were in the first study 2,000 IU/animal, in the second study 10,000 IU/animal, and in the third study 40,000 IU/animal; HX575 revealed a good local tolerability in rabbits at all tested routes of administration; also the dogs in the 13-week subchronic toxicity study with HX575 and Erypo® revealed no signs of local intolerance reaction.	No safety concern apparent.
Immunotoxicity/antigenicity	
Studies performed by Sandoz: the immunotoxicity of HX575 drug product was examined in the 13-week repeated dose toxicity study, which showed anti- epoetin antibodies in one dose group, and in a PK/PD study in dogs, where no anti-epoetin anti- bodies were detected.	Antigenic potential was addressed during the clinical development programme.
Mechanism of drug interaction	
Mechanism of drug interaction: No own studies were performed by Sandoz; no evidence exists that indicates that treatment with epoetin alfa alters the metabolism of other drugs; drugs that decrease erythropoiesis may decrease the response to epoetin alfa; since cyclosporine is bound by RBCs there is potential for a drug interaction. If epoetin alfa is given concomitantly with cyclosporine, blood levels of cyclosporine should be monitored and the dose of	No risk beyond that of the reference drug is anticipated.

Key Safety Findings (From non-clinical studies)	**Relevance to human usage**
cyclosporine adjusted as the hematocrit rises; no evidence exists that indicates an interaction between epoetin alfa and G-CSF or GMCSF (G- or GM-colony-stimulating factors) with regard to hematological differentiation or proliferation of tumor biopsy specimens *in vitro*.	
General safety pharmacology	
General safety pharmacology: no own studies were performed by Sandoz; no remarkable or clinically important adverse pharmacological effect was discerned with the reference product that would prohibit human use	No safety concern apparent.

Conclusions on non-clinical data: There are no safety concerns on HX575 that are different from Erypo®/Eprex®. The non-clinical safety profile is comparable to that of the reference product.

Part II: Module SIII - Clinical trial exposure

Safety and efficacy data are available from the pre-authorization phase, i.e. Phase I and Phase III clinical trials and from the post-authorization phase (Phase IV clinical trials). HX575 was approved as biosimilar to reference epoetin alfa in 2006 for most indications, in 2016 for s.c. administration with syringe in anemia related to CRF and in 2018 for anemia of certain MDS. Efficacy should not be expected to differ between reference and biosimilar either, as the common goal of epoetin treatment is to expand the pool of RBC, whether in a context of anemia or as preparation for high-hemorrhage-risk surgery, and the benefit in patients is mediated through the same interaction of epoetin alfa with the EPO receptor irrespective of the precise indication. An overview of the clinical studies contributing to the safety and efficacy of HX575 is provided in Table 3.

Table 3 Overview of clinical studies contributing to efficacy and safety data of HX575

Phase	Population	Study number	Dialysis status	Administration route	Administration device
III	CKD	INJ-9 part I	On dialysis	i.v.	PFS
	CKD	INJ-9 part II	On dialysis	i.v.	PFS
	CKD	INJ-14	On dialysis or pre-dialysis	i.v.	PFS
	CKD	INJ-17	Pre-dialysis	s.c.	PFS
	CKD stage 5	HX575-307	On dialysis	s.c.	vial
	CKD	HX575-308	On dialysis or pre-dialysis	s.c.	PFS
	Cancer	INJ-11	On chemotherapy	s.c.	PFS
I	Healthy volunteers	INJ-4	-	i.v. + s.c.	PFS
	Healthy volunteers	INJ-5	-	i.v.	PFS
	Healthy volunteers	HX575-106	-	i.v.	PFS
	Healthy volunteers	INJ-6	-	s.c.	PFS
	Healthy volunteers	INJ-7	-	s.c.	PFS
	Healthy volunteers	INJ-12	-	s.c.	PFS
	Healthy volunteers	HX575-110	-	s.c.	vial
	Healthy volunteers	HX575-111	-	s.c.	vial

CKD=chronic kidney disease; i.v.=intravenous; PFS=pre-filled syringe; s.c.=subcutaneous

The safety data base generated in the clinical trials cannot have detected very rare events such as PRCA. The observation of these very rare side effects is only feasible in a large post-approval pharmacovigilance program. In addition, due to the similar safety profile of HX575 with Erypo®/Eprex® in the clinical development program, a comparable safety profile to the reference product is also expected to be demonstrated by the post-approval pharmacovigilance program for these very rare side effects.

During the clinical development program, 1756.9 subject years exposure to HX575 was obtained in 3027 patients. Including the healthy volunteers in the phase I studies, 1783.3 subject years exposure were obtained in 3480 subjects (Table 4). Hereby, 74 cancer patients on chemotherapy treated s.c. contributed 11.1 patient-years, 807 CKD patients treated s.c. contributed 646.8 subject years and 2146 CKD patients treated i.v. contributed 1099.0 subject years (Table 5).

Table 4 Duration of exposure in all subjects

Duration	Patients (N=3027)			Healthy volunteers (N=453)		All subjects (N=3480)	
	Subjects n (%)		Subject years	Subjects n (%)	Subject years	Subjects n (%)	Subject years
< 1 month	122 (4.0)	5.2	453 (100.0)	26.5	575 (16.5)	31.7	
1 - <3 months	221 (7.3)	38.2			221 (6.4)	38.2	
3 - <6 months	871 (28.8)	388.5			871 (25.0)	388.5	
6 - <12 months	1517 (50.1)	1013.2			1517 (43.6)	1013.2	
12- <15 months	296 (9.8)	311.7			296 (8.5)	311.7	
Total	3027 (100.0)	1756.9	453 (100.0)	26.5	3480 (100.0)	1783.3	

N=number of subjects in each treatment group; n=number of subjects per category in each treatment group.

Subject years is the sum of each subject's treatment exposure. Each subject's treatment exposure is calculated as (Date of last dose – date of first dose + 1)/365.25 per administration route.

Table 5 Duration of exposure in all patients by indication and administration route

	HX575 s.c., cancer (N=74)		HX575 s.c., CKD (N=807)		HX575 i.v., CKD (N=2146)		Patients (N=3027)	
Duration	Subjects n (%)	Subject years	Subjects n (%)	Subject years	Subjects n (%)	Subject years	Subjects n (%)	Subject years
<1 month	18 (24.3)	0.9	26 (3.2)	1.0	78 (3.6)	3.4	122 (4.0)	5.2
1 - <3 months	56 (75.7)	10.2	40 (5.0)	6.6	125 (5.8)	21.4	221 (7.3)	38.2
3 - <6 months			84 (10.4)	33.7	787 (36.7)	354.8	871 (28.8)	388.5
6 - <12 months			569 (70.5)	515.6	948 (44.2)	497.5	1517 (50.1)	1013.2
12 - <15 months			88 (10.9)	89.9	208 (9.7)	221.9	296 (9.8)	311.7
Total	74 (100.0)	11.1	807 (100.0)	646.8	2146 (100.0)	1099.0	3027 (100.0)	1756.9

N=number of subjects in each treatment group; n=number of subjects per category in each treatment group.

Subject years is the sum of each subject's treatment exposure. Each subject's treatment exposure is calculated as (Date of last dose – date of first dose + 1)/365.25 per administration route.

Table 6 Exposure by age group and gender (patients)

Age group (years)	Sex	HX575 s.c., cancer (N=74)		HX575 s.c., CKD (N=807)		HX575 i.v., CKD (N=2146)		Patients (N=3027)	
		Subjects n (%)	Subject years	Subjects n (%)	Subject years	Subjects n (%)	Subject years	Subjects n (%)	Subject years
18-<40	Total	3 (4.1)	0.5	136 (16.9)	115.7	205 (9.6)	105.3	344 (11.4)	221.5
	Male	1 (1.4)	0.2	76 (9.4)	68.8	132 (6.2)	70.7	209 (6.9)	139.7
	Female	2 (2.7)	0.3	60 (7.4)	46.9	73 (3.4)	34.6	135 (4.5)	81.8
40-<75	Total	66 (89.2)	9.9	546 (67.7)	436.1	1461 (68.1)	759.0	2073 (68.5)	1205.0
	Male	32 (43.2)	4.9	271 (33.6)	213.4	835 (38.9)	433.4	1138 (37.6)	651.6
	Female	34 (45.9)	5.1	275 (34.1)	222.7	626 (29.2)	325.6	935 (30.9)	553.4
>=75	Total	5 (6.8)	0.7	125 (15.5)	95.0	480 (22.4)	234.7	610 (20.2)	330.3
	Male			63 (7.8)	48.0	250 (11.6)	119.1	313 (10.3)	167.1
	Female	5 (6.8)	0.7	62 (7.7)	47.0	230 (10.7)	115.6	297 (9.8)	163.3
Total	Total	74 (100.0)	11.1	807 (100.0)	646.8	2146 (100.0)	1099.0	3027 (100.0)	1756.9
	Male	33 (44.6)	5.1	410 (50.8)	330.2	1217 (56.7)	623.2	1660 (54.8)	958.4
	Female	41 (55.4)	6.0	397 (49.2)	316.6	929 (43.3)	475.8	1367 (45.2)	798.4

N=number of subjects in each treatment group; n=number of subjects per category in each treatment group

Subject years is the sum of each subject's treatment exposure. Each subject's treatment exposure is calculated as (Date of last dose – date of first dose + 1)/365.25 per administration route.

Table 7 Exposure by dose (patients)

Exposure IU/week	HX575 s.c., cancer (N=74)		HX575 s.c., CKD (N=807)		HX575 i.v., CKD (N=2146)		Patients (N=3027)	
	Subjects n (%)	Subject years	Subjects n (%)	Subject years	Subjects n (%)	Subject years	Subjects n (%)	Subject years
≤3000			219 (27.1)	183.3	306 (14.3)	147.0	525 (17.3)	330.3
3000 - ≤6000			344 (42.6)	279.6	781 (36.4)	410.6	1125 (37.2)	690.2
6000 - ≤9000			143 (17.7)	107.9	512 (23.9)	270.6	655 (21.6)	378.5
9000 - ≤12000			47 (5.8)	36.8	270 (12.6)	140.4	317 (10.5)	177.2
>12000	74 (100.0)	11.1	54 (6.7)	39.2	277 (12.9)	130.2	405 (13.4)	180.6
Total	74 (100.0)	11.1	807 (100.0)	646.8	2146 (100.0)	1099.0	3027 (100.0)	1756.9

CKD=chronic kidney disease; i.v.=intravenous; IU=international units; n=number of subjects in each treatment group; s.c.=subcutaneous

Subject years is the sum of each subject's treatment exposure. Each subject's treatment exposure is calculated as (Date of last dose – date of first dose + 1)/365.25 per administration route.

Table 8 Exposure by race (patients)

Race	**HX575 s.c., cancer (N=74)**		**HX575 s.c., CKD (N=807)**		**HX575 i.v., CKD (N=2146)**		**Patients (N=3027)**	
	Subjects n (%)	**Subject years**	**Subjects n (%)**	**Subject years**	**Subjects n (%)**	**Subject years**	**Subjects n (%)**	**Subject years**
White/ Caucasian	74 (100.0)	11.1	722 (89.5)	575.7	2120 (98.8)	1088.5	2916 (96.3)	1675.3
Black Or African American			57 (7.1)	48.5	7 (0.3)	2.7	64 (2.1)	51.2
Asian			12 (1.5)	8.4	1 (0.0)	1.1	13 (0.4)	9.5
American Indian Or Alaska Native			11 (1.4)	10.3			11 (0.4)	10.3
Native Hawaiian Or Other Pacific Islander			4 (0.5)	3.3			4 (0.1)	3.3
Oriental					9 (0.4)	3.2	9 (0.3)	3.2
Other					9 (0.4)	3.5	9 (0.3)	3.5
Unknown			1 (0.1)	0.5			1 (0.0)	0.5

N=number of subjects in each treatment group; n=number of subjects per category in each treatment group

Subject years is the sum of each subject's treatment exposure. Each subject's treatment exposure is calculated as (Date of last dose – date of first dose + 1)/365.25 per administration route.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

HX575 was developed as a biosimilar to Erypo®/Eprex® with an adequate biosimilar clinical development program. The safety and efficacy profile of HX575 is similar to the reference product Erypo®/Eprex®.

In the development of HX575 as a similar biological medicinal product, four Phase III studies were conducted in patients with chronic kidney disease (hemodialysis patients, study INJ-9, part I and II, or dialysis not restricted to one type, HX575-307; pre-dialysis patients, INJ-17; or both pre-dialysis and dialysis patients, HX575-308) and one Phase III trial was conducted in cancer patients (INJ-11). Also, data from a Phase IV post-authorization studies in patients with HX575 are available.

The exclusion criteria (see Table 9) mostly pertain to known contraindications or warnings for epoetin alfa. These exclusion criteria do not constitute a significant lack of information for the target population of epoetin alfa.

No HX575 clinical study in CKD patients has included children. However, conditions for use in this population, in peritoneal or hemodialysis, are descried, based on i.v. and some s.c. Eprex® studies in children, and are specified in various sections of the Binocrit SmPC.

Based on the established safety profile for the reference product Erypo®/Eprex®, no significant risks are expected for populations not studied directly with HX575 poetic alfa.

Table 9 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
General criteria			
Anemia of non-renal causes, primary hematologic disorders	Not part of approved indications, clear definition of patient population for trials conducted in anemia either related to CKD or to chemotherapy for cancer.	No	No direct concern about safety with epoetin alfa. Used for trial optimization Reference can be found in Section 4.4 of SmPC Binocrit/Abseamed/Epoetin alfa HEXAL. Such conditions should be identified and treated before treatment, if possible, as they can interfere with effectiveness of the treatment.
Known history of bone marrow disease	Epoetin alfa stimulates bone marrow to increase red blood cells production. Disease of bone marrow might interfere with efficacy of HX575.	No	Reference can be found in Section 4.4 of SmPC Binocrit/Abseamed/Epoetin alfa HEXAL

Criteria	**Reason for exclusion**	**Is it considered to be included as missing information?**	**Rationale**
Insufficient concomitant iron treatment	Iron deficiency might interfere with efficacy of HX575.	No	All other causes of anemia (including iron deficiency) should be evaluated and treated prior to initiating therapy with epoetin alfa. Details can be found in Sections 4.2 and 4.4 of the
Evidence of severe hepatic dysfunction	Epoetin alfa should be used with caution in patients with chronic liver failure.	No	Adequate warning for caution can be found in Section 4.4 of SmPC Binocrit/Abseamed/Epoetin alfa HEXAL
Current uncontrolled hyperparathyroidism	Hyperparathyroidism occurs as a frequent complication of CKD and interferes with anemia correction if not properly controlled.	No	Not related to safety concerns of HX575, used for trial optimization only.
Uncontrolled hypertension	Hypertension is an undesirable effect of HX575, which is contraindicated in patients with uncontrolled hypertension.	No	Listed as contraindication in Section 4.3 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL. Adequate warning listed in Section 4.4 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL to discontinue HX575 treatment in case blood pressure cannot be controlled.
Congestive heart failure New York Heart Association class III and IV	Major cardiovascular events (including congestive heart failure) cases occurred during epoetin alfa treatment in clinical trials.	No	Details can be found in Section 5.1 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Unstable angina pectoris, or cardiac infarction or cerebrovascular event prior to screening	HX575 is contraindicated in patients with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including patients with recent myocardial infarction or cerebral vascular accident.	No	Listed as contraindication in Section 4.3 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.

Criteria	**Reason for exclusion**	**Is it considered to be included as missing information?**	**Rationale**
History of blood coagulation disease	Increased risk of thromboembolic events was identified associated with erythropoietin treatment.	No	Thrombotic vascular events risk is mentioned in Section 4.4 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL as to be monitored in all patients with special warning in case of previous such history.
Thrombocytopenia, leukopenia	Avoiding confounding or bias of safety or efficacy data.	No	Not related to safety concerns of HX575, used for trial optimization only.
Active gastrointestinal bleeding prior to study participation	Blood loss might interfere with efficacy of HX575.	No	All other causes of anemia (including blood loss) should be evaluated and treated prior to initiating therapy with epoetin alfa. Details can be found in Section 4.4 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Patients receiving any RBC/whole blood transfusion	Transfusion was excluded to avoid confounding or bias in efficacy data.	No	Epoetin alfa administration has been shown to increase hemoglobin and decrease transfusion requirements.
Evidence of acute infectious disease or serious active	Broader range of infections was excluded as necessary by contraindications to avoid confounding or bias of safety and efficacy data.	No	Infections which are not severe are expected to be controlled by appropriate clinical measures. Inflammation can cause anemia with unresponsiveness to epoetin and is to be treated before initiating HX575 treatment as referenced in Section 4.4 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Inflammatory states within one month before screening or during the screening/baseline period	Broader range of infections was excluded as necessary by contraindications to avoid confounding or bias of safety and efficacy data.	No	Inflammation can cause anemia with unresponsiveness to epoetin and is to be treated before initiating HX575 treatment as referenced in Section 4.4 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Suspicion or known PRCA	Patients who develop pure red cell aplasia (PRCA) following treatment with any erythropoietin should not receive HX575 or any other erythropoietin.	No	PRCA under any prior ESA treatment is a listed contraindication to HX575 (Section 4.3 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.

Criteria	**Reason for exclusion**	**Is it considered to be included as missing information?**	**Rationale**
History of PRCA or aplastic anemia	PRCA or aplastic anemia whether or not under previous ESA treatment, may reflect an immune condition posting a risk for ESA-induced PRCA.	No	No data available about HX575 treatment in patients with prior PRCA or aplastic anemia, however PRCA under any prior ESA treatment is a listed contraindication to HX575 (Section 4.3 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL
History of anti-EPO antibodies	Neutralizing anti-epoetin antibody-mediated PRCA has been reported after epoetin treatment mainly in chronic renal failure patients. Binding antibodies that are not neutralizing epoetin have not been associated with PRCA. Exclusion of patients with prior anti-epoetin antibodies regardless if they were binding or neutralizing, was used in some trials as a broader safety precaution to avoid any controllable risk.	No	Anti-epoetin antibodies are not a contraindication to HX575 usage if they are not associated with a loss of efficacy and PRCA.
Pregnancy or women of childbearing potential with no effective birth control	Lack of data for safe use during pregnancy.	No	There are no or limited amount of data about the use of epoetin alfa in pregnant women.
Lactating women	Lack of data for safe use during lactation.	No	There are no or limited amount of data about the use of epoetin alfa in lactating women.
Known history of severe drug-related allergies	Avoid confounding or bias of safety or efficacy data.	No	Not related to safety concerns of HX575, used for trial optimization only.
Known allergy to one of the ingredients of the test or reference products or hypersensitivity to mammalian-derived products	HX575 is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.	No	Listed as contraindication in Section 4.3 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Previously diagnosed HIV or acute hepatitis infection	Avoid confounding or bias of safety or efficacy data of complex chronic	No	Apart from hepatitis C, not related to safety concerns of HX575, used for trial optimization only.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	diseases. Also, PRCA cases have been reported in patients with hepatitis C treated with interferon and ribavirin, when ESAs are used concomitantly. Epoetin alfa is not approved in the management of anemia associated with hepatitis C.		Information about hepatitis C can be found in Section 4.4 of SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
History or treatment of epilepsy, or epileptic seizures	Epoetin alfa should be used with caution in patients with epilepsy, history of seizures, or medical conditions associated with a predisposition to seizure activity.	No	Mentioned among special warnings in Section 4.4 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Therapy with immunosuppressants or any drug known to affect the hematocrit	Concomitant medication might interfere with efficacy of HX575.	No	Medicinal products that decrease erythropoiesis may decrease the response to epoetin alfa. Details can be found in Section 4.5 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Clinical evidence of malignant diseases	Erythropoietin receptors may be expressed on the surface of a variety of tumor cells.	No	The role of ESAs on disease progression or reduced progression-free survival cannot be excluded. Details can be found in Section 4.4 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
INJ-9			
Overt bleeding within 2 months of inclusion or hemolysis	Blood loss might interfere with efficacy of HX575.	No	All other causes of anemia (including blood loss) should be evaluated and treated prior to initiating therapy with epoetin alfa. Details can be found in Section 4.4 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Any androgen therapy within two months before screening and during the study	Androgen therapy has the potential to reverse anemia linked to certain types of hematological disorders. Avoid	No	Not related to safety concerns of HX575, used for trial optimization only.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	confounding or bias of efficacy data.		
INJ-11			
Patients who receive curative intended chemotherapy	Study was performed in selected population of cancer patients receiving palliative chemotherapy and suffering from chemotherapy associated anemia.	No	Not related to safety concerns of HX575, used for trial optimization only.
Known primary or metastatic malignancy of the CNS or bone marrow	Erythropoietin receptors may be expressed on the surface of a variety of tumor cells.	No	The role of ESAs on disease progression or reduced progression-free survival cannot be excluded. Details can be found in Section 4.4 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Thrombotic events during the last 6 months	Increased risk of thromboembolic events was identified to be associated with erythropoietin treatment.	No	Mentioned among special warnings in Section 4.4 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Transfusion of white blood cells or packed red blood cells (more than 2 packs) within 4 weeks and any transfusion or white blood cells or packed red blood cells within 2 weeks prior to randomization	Transfusion was excluded to avoid confounding or bias of efficacy data.	No	Epoetin alfa administration has been shown to increase hemoglobin and decrease transfusion requirements. In cell cultures of human bone marrow cells, epoetin alfa stimulates erythropoiesis specifically and does not affect leucopoiesis. Details can be found in Sections 5.1 and 5.3 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Erythropoietin or darbepoetin therapy within 8 weeks before screening	Avoid confounding or bias of safety or efficacy data.	No	Used for trial optimization only.
Radiation therapy during the study	In clinical trials with epoetin alfa decreased locoregional control was observed in patients with advanced head and neck cancer receiving radiation therapy.	No	Details can be found in Section 4.4 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.

Criteria	**Reason for exclusion**	**Is it considered to be included as missing information?**	**Rationale**
Radiation-induced anemia	Radiation-induced anemia might interfere with efficacy of HX575.	No	All other causes of anemia should be evaluated and treated prior to initiating therapy with epoetin alfa. Details can be found in Section 4.4 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Therapy with cyclosporine	Since cyclosporin is bound RBCs there is potential for a medicinal product interaction.	No	If epoetin alfa is given concomitantly with cyclosporin, blood levels of cyclosporine should be monitored and the dose of cyclosporine adjusted as the hematocrit rises. Information about potential for this interaction can be found in Section 4.5 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Chemotherapy which causes predictable treatment with peripheral blood progenitor therapy, such as G-CSF	Avoid confounding or bias of safety or efficacy data.	No	Not related to safety concerns of HX575, used for trial optimization only.
Major surgery within the last 14 days prior to randomization	Avoid confounding or bias of safety or efficacy data.	No	Not related to safety concerns of HX575, used for trial optimization only.
INJ-14			
Systemic immunosuppressive medication or any other drugs known to adversely affect the hemoglobin level	Concomitant medication might interfere with efficacy of HX575.	No	Medicinal products that decrease erythropoiesis may decrease the response to epoetin alfa. Details can be found in Section 4.5 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Known primary lack of efficacy, unexplained loss of effect to an ESA	Development of lack of efficacy can be clinical sign of epoetin-related PRCA.	No	Details can be found in Section 4.4 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Has any form of psychiatric disorder which may invalidate communication	Avoid confounding or bias of safety or efficacy data.	No	Not related to safety concerns of HX575, used for trial optimization only.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Cannot receive adequate antithrombotic prophylaxis for any reason	HX575 is contraindicated for surgery patients who cannot receive adequate antithrombotic prophylaxis for any reason.	No	Listed as contraindication in Section 4.3 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL
INJ-17			
Therapy with immunosuppressants (other than corticosteroids for chronic treatment) for patients with renal allograft or other chronic conditions (e.g., lupus erythematosus, rheumatic arthritis)	Concomitant medication might interfere with efficacy of HX575.	No	Medicinal products that decrease erythropoiesis may decrease the response to epoetin alfa. Details can be found in Section 4.5 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Patients previously treated with chronic dialysis within the last 6 months (exception: one session of acute dialysis)	Study targeted anemia patients associated with chronic renal insufficiency in pre-dialysis stage.	No	Not related to safety concerns of HX575, used for trial optimization only.
Patients with acute deterioration of renal function during the screening phase according to the investigator's judgment	Study targeted anemia patients associated with chronic renal insufficiency in pre-dialysis stage.	No	Not related to safety concerns of HX575, used for trial optimization only.
Uncontrolled diabetes mellitus (HbA1c > 10% at Visit -2)	Avoid confounding or bias of safety or efficacy data.	No	Not related to safety concerns of HX575, used for trial optimization only.
History of stroke or myocardial infarction	HX 575 is contraindicated in patients with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including patients with recent myocardial infarction or cerebral vascular accident.	No	Listed as contraindication in Section 4.3 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Ongoing treatment with phenprocoumon or other cumarin derivatives	Avoid confounding or bias of safety or efficacy data.	No	No evidence exists that indicates that treatment with epoetin alfa alters the metabolism of other medicinal products.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Acute or chronic infection by a C-reactive protein value of > 30 mg	Broader range of infections or active inflammatory diseases were excluded as necessary to avoid confounding or bias of safety data.	No	Used for trial optimization only.
Planned major surgery (with expected high blood loss) during the next 3 months or major surgery within the previous 3 months (except laser photocoagulation, access surgery)	Avoid confounding or bias of safety or efficacy data.	No	Used for trial optimization only.
Known or suspicion of any non-compliance with respect to subcutaneous treatment	Study was designed to evaluate the safety and immunogenicity of subcutaneous epoetin alfa; non-compliance can result in confounding or bias of study data.	No	Used for trial optimization only.
HX575-307 and HX575-308			
Patients who for any reason cannot receive adequate antithrombotic prophylaxis	HX575 is contraindicated for surgery patients who cannot receive adequate antithrombotic prophylaxis for any reason.	No	Listed as contraindication in Section 4.3 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Positive result for binding anti-EPO antibodies in the RIP assay	Antibody-mediated PRCA has been reported after epoetin treatment mainly in chronic renal failure patients.	No	Details can be found in Section 4.4 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Lack of efficacy or unexplained loss of effect of a previous ESA therapy	Development of lack of efficacy can be clinical sign of epoetin-related PRCA.	No	Details can be found in Section 4.4 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.

Criteria	**Reason for exclusion**	**Is it considered to be included as missing information?**	**Rationale**
Planned major surgery during the duration of the study (including living donor kidney transplantation, excluding deceased donor kidney transplantation)	Avoid confounding or bias of safety or efficacy data.	No	Used for trial optimization only.
Evidence of cirrhosis	Epoetin alfa should be used with caution in patients with chronic liver failure. The safety of epoetin alfa has not been established in patients with hepatic dysfunction.	No	Reference can be found in Section 4.4 of SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Serum albumin <3 g/dL	There is no identified risk with hypalbuminemia, however, can be caused by several different diseases. Condition is excluded to avoid confounding or bias of safety or efficacy data.	No	Used for trial optimization only.
Known HIV or Hepatitis B infection	Avoid confounding or bias of safety or efficacy data.	No	Not related to safety concerns of HX575, used for trial optimization only.
Hepatitis C infection on an active treatment	PRCA cases have been reported in patients with hepatitis C treated with interferon and ribavirin, when ESAs are used concomitantly. Epoetin alfa is not approved in the management of anemia associated with hepatitis C.	No	Information about hepatitis C can be found in Section 4.4 of SmPC Binocrit/Abseamed/Epoetin alfa HEXAL
Percutaneous coronary intervention, or coronary artery bypass grafting during the last 6 months prior to randomization	HX 575 is contraindicated in patients with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including patients with recent myocardial infarction or cerebral vascular accident.	No	Listed as contraindication in Section 4.3 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.

Criteria	**Reason for exclusion**	**Is it considered to be included as missing information?**	**Rationale**
History of vascular thrombosis (large arteries or veins) (excluding vascular access thrombosis)	HX 575 is contraindicated in patients with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including patients with recent myocardial infarction or cerebral vascular accident.	No	Listed as contraindication in Section 4.3 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years	Erythropoietin receptors may be expressed on the surface of a variety of tumor cells.	No	The role of ESAs on disease progression or reduced progression-free survival cannot be excluded. Details can be found in Section 4.4 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL
Systemic lupus erythematosus	Avoid confounding or bias of safety or efficacy data.	No	Not related to safety concerns of HX575, used for trial optimization only.
Patient treated with systemic immunosuppressive therapy for more than 4 weeks during 2 months prior to randomization	Concomitant medication might interfere with efficacy of HX575.	No	Medicinal products that decrease erythropoiesis may decrease the response to epoetin alfa. Details can be found in Section 4.5 of the SmPC Binocrit/Abseamed/Epoetin alfa HEXAL.
Use of erythropoiesis-stimulating agents other than Epogen® or Procrit® during 2 months prior to randomization	Avoid confounding or bias of safety or efficacy data.	No	Not related to safety concerns of HX575, used for trial optimization only.
Use of investigational drugs within 30 days or 5 half-lives prior to first screening visit, whichever is longer	Avoid confounding or bias of safety or efficacy data.	No	Not related to safety concerns of HX575, used for trial optimization only.

Exclusion criteria were in agreement with the corresponding reference SmPC Erypo®/ Eprex® during the years of conducting the clinical trials. Additional exclusion criteria were necessary to allow a reliable, unbiased assessment of the efficacy and safety endpoints of the clinical trials.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development program was conducted in patients with anemia related to CKD, and in patients with chemo-induced anemia during cancer treatment and in healthy volunteers. It is unlikely to detect certain types of adverse reactions either because they are rare, adverse reactions with a long latency, those caused by prolonged or cumulative exposure or those specific to other indications not assessed in HX575 pivotal trials such as auto-donation/presurgery, anemia in children in hemodialysis and anemia related to MDS.

However, these types of adverse reactions could be detected during the more extensive clinical development and post-marketing experience of the reference drug. The established safety profile of the originator is also applicable for the biosimilar.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Children

There is no clinical trial experience with HX575 in children.

In line with the Pediatric Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for pediatric use, HX575, as similar biological medicinal product, is exempted from the requirement to submit a Pediatric Investigational Plan (PIP).

The use of HX575 is not approved in the pediatric population below the age of 18 years in oncological or hematological (such as MDS) indications. However, HX575 like epoetin alfa is indicated for the treatment of symptomatic anemia associated with CRF in adults, and in children aged 1 to 18 years on hemodialysis.

However, there is a potential for off-label use, especially in 'anemia due to chemotherapy' indications. Experience in children with anemia of CKD in Hemodialysis was available for the reference product which is indicated in this population. Any differences between children and adults are expected to be the same as for the reference product Erypo®/Eprex®.

Elderly

Clinical trial experience in elderly subjects is extensive as 20.2% subjects of the overall clinical trial population were at least 75 years of age (Table 6). Across all development studies in 2 different indications, the treatment benefit was similar in patients independent of age. While Sandoz did not perform general pharmacology studies for safety, however PK properties of HX575 and Erypo®/Eprex® are similar. Following the information available for the reference product, no dose adjustment is required for HX575 in elderly.

- Use in different age ranges: No special precautions for different age ranges ≥18 years, > 65, >75.
- Need for laboratory screening prior to use: No specific requirements.
- Effect of multiple co-existing impairments: No specific information available.
- ADRs of special concern: No specific ADR of special concern in elderly.

- Effect of multiple medications: No dose adjustment recommended.

Pregnant or lactating women

No clinical experience with HX575 in pregnant or lactating women is available. There are no adequate data from the use of epoetin alfa in pregnant or lactating women.

Studies in animals have shown reproductive toxicity. Consequently, in chronic renal failure patients epoetin alfa should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Patients with renal and hepatic impairment

Most of the CRF patients who participated in HX575 clinical trials suffered from end-stage renal disease. Studies INJ-9, INJ-14, INJ-17, HX575-307 and HX575-308 did not exclude patients with cardiovascular diseases, hypertension, diabetes mellitus, hyperparathyroidism and glomerulonephritis at baseline.

No clinical experience with HX575 in patients with hepatic impairment. The safety of epoetin alfa has not been established in patients with hepatic dysfunction. HX575 should be used with caution in patients with chronic liver failure.

Patients with other relevant co-morbidity

- Cardiovascular

Patients with the following cardiac conditions were excluded from some studies:

- Congestive heart failure New York Heart Association class III and IV
- Unstable angina pectoris, active cardiac disease
- Cardiac infarction during the last six months before visit 1

The use of HX575 is contraindicated in such patients due to concern for cardiac complications of hypervolemia in healthy volunteers, hypovolemia or risks for cardiac ischemia in subjects and were necessary to allow a reliable, unbiased efficacy assessment.

Patients with a disease severity different from the inclusion criteria in the clinical trial population

The anemia or disease severity in patients, is representative for the target population and recommended treatment criteria.

Sub-populations carrying known and relevant polymorphisms

No clinical experience with HX575 in patient sub-populations with genetic polymorphisms is available. No specific testing for any pharmacogenetics marker is recommended in the SmPC Eprex®.

Patients of different racial and/or ethnic origin

There is clinical experience with HX575 in CKD patients of different races, however with a vast majority of white subjects 96.3% (Table 8). No difference in the safety profile of HX575 in different ethnic origins is expected to that of the reference product Erypo®/Eprex®.

Table 10 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Lactating women	Not included in the clinical development program
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with different race	Not controlled in the clinical development program; refer to Table 8 for race distribution.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Patients 65 or greater years of age	Included this age group in the clinical development program; refer to Table 6 for age distribution

Part II: Module SV - Post-authorization experience

SV.1 Post-authorization exposure

SV.1.1 Method used to calculate exposure

An estimate of patient exposure is cumulatively calculated based on worldwide sales volume in International Unit (IU) of active substance sold (includes data from Sandoz (including Hexal AG), Novartis and license partner Medice Arzneimittel Putter GmbH & Co KG). One microgram is approximately 119 IU. Epoetin alfa dose varies based on indication, patient age group, Hb levels and route of administration. Epoetin alfa is not dosed daily in recommended use. An average dose has been deduced based on assumptions of an average weight of 70 kg, a dose of 50 IU/kg, three times per week as the labelled starting dose based on the most common indication for use (anemia due to End Stage Renal Disease); this dose falls within the recommended weekly maintenance dose which is between 75 IU/kg and 300 IU/kg. Therefore, a defined weekly dose as per these assumptions and the label would be approximately 10500 IU/week (70 kg × 150 IU/kg) and upon calculation defined daily dose is considered as 1500 IU/day.

The estimated Patient Treatment Years (PTY) were calculated based on the below formula:

Formula: PTY= Amount sold in IU / [Defined daily dose (1500)*365]

SV.1.2 Exposure

- **Sandoz:**

Table 11 Cumulative exposure to Binocrit (HX575)/Abseamed and Epoetin Alfa from marketing experience

	EEA (Patient treatment years)	**ROW (Patient treatment years)**
Epoetin alfa, solution for injection	1,733,769	402,418

EEA=European Economic Area; ROW=Rest of the World.
This table includes cumulative data obtained from 01-Jan-2007 to 30-April-2024.
Source of data: Worldwide sales volume

- **Partner Exposure:**
  - **Novartis:**

Table 12 Cumulative exposure to Binocrit (HX575)/Abseamed and Epoetin Alfa from marketing experience

	EEA (Patient treatment years)	**ROW (Patient treatment years)**
Epoetin alfa, solution for injection	9327	0

EEA=European Economic Area; ROW=Rest of the World.

This table includes cumulative data obtained till 30-April-2024.
Source of data: Worldwide sales volume

– **Medice Arzneimittel Pütter GmbH & Co. KG:**

Table 13 Cumulative exposure to Binocrit (HX575)/Abseamed and Epoetin Alfa from marketing experience

	EEA (Patient treatment years)	**ROW (Patient treatment years)**
Epoetin alfa, solution for injection	197,073	84

EEA=European Economic Area; ROW=Rest of the World.
This table includes cumulative data obtained from 01-Jan-2007 to 30-April-2024.
Source of data: Worldwide sales volume

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

The misuse of recombinant human erythropoietin in sports is well known. 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. Misuse can lead to serious health risks for athletes. It is well known that recombinant human erythropoietin, by increasing the number of red blood cells and blood viscosity, leads to an increased risk of heart disease, stroke, and cerebral or pulmonary embolism. Recombinant human erythropoietin has been recognized and banned as a performance-enhancing substance since the early 1990s. There is a lot of information available with respect to misuse of recombinant human erythropoietin in sports (World Anti-Doping Code). During the reporting period of International Birth Date to 30-Apr-2024, no cases reporting on intentional product misuse of epoetin alfa were noted on medical review of cases in safety database.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

This section is not applicable; the RMP was already approved.

SVII.2 New safety concerns and re-classification with a submission of an updated RMP

The RMP of the reference product Eprex® available is version 6.0.

The important identified risk: Pure red cell aplasia and important potential risks: Disease progression and Survival impact are removed as per PRAC Rapporteur's assessment report on RMP version 19.0 under procedure EMEA/H/C/WS2615. The rationale for the removal of safety concerns is that the risks are adequately characterised and addressed appropriately via routine pharmacovigilance activities and hence there is no need for further risk minimisation activities and no further evaluation as a part of pharmacovigilance plan. Safety concerns are removed in alignment with the EU RMP template as per the GVP module V revision 2.

SVII.3 Details of important identified risks, important potential risks, and missing information

The adverse reactions observed in the clinical trials conducted with HX575 are well known for epoetin treatment and similar to those of the reference product Erypo®/Eprex®. There are no ongoing issues concerning the risks of erythropoietin treatment.

No new or unlisted adverse drug reactions were observed in Phase III trials with HX575. No other special risks or potential risks were identified during the development of HX575. No new or unknown adverse events or adverse drug reactions were observed in any post-authorization study.

Part II: Module SVIII - Summary of the safety concerns

Table 14 SVIII.1: Summary of safety concerns

Important identified risk	None
Important potential risk	None
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

The Global Pharmacovigilance System ensures the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country, along with routine PV activities.

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Routine pharmacovigilance activities are in place.

III.2 Additional pharmacovigilance activities

There are no additional pharmacovigilance activities new or ongoing for Epoetin Alfa.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorization efficacy studies

There are no planned post-authorization efficacy studies.

Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

The safety information in the current product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimization Measures

Routine risk minimization measures are in place.

V.2. Additional Risk Minimization Measures

Not applicable.

V.3. Summary of risk minimization measures

Not applicable.

Part VI: Summary of the risk management plan

Summary of risk management plan for Abseamed®, Binocrit®, Epoetin alfa Hexal® (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 Abseamed®/ Binocrit®/ Epoetin alfa Hexal®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.

Part VI: I. The medicine and what it is used for

Abseamed®/ Binocrit®/ Epoetin alfa Hexal® is indicated for the treatment of symptomatic anemia:

• Associated with 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 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 the benefits of Abseamed®/ Binocrit®/ Epoetin alfa Hexal® can be found in the respective EPARs, including the plain-language summaries, available on the EMA website, under the medicines' webpages:
https://www.ema.europa.eu/en/medicines/human/EPAR/abseamed
https://www.ema.europa.eu/en/medicines/human/EPAR/binocrit
https://www.ema.europa.eu/en/medicines/human/EPAR/epoetin-alfa-hexal

Part VI: II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet 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 minimise its risks.

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

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

Part VI: II.A 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 15 List of important risks and missing information

Important identified risk	None
Important potential risk	None
Missing information	None

Part VI: II.B Summary of important risks

The safety information in the current Product Information is aligned to the reference medicinal product.

Part VI: II.C Post-authorization development plan

Part VI: II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization.

Part VI: II.C.2 Other studies in post-authorization development plan

There are no studies required for Abseamed®/ Binocrit®/ Epoetin alfa Hexal®.

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 5 - Protocols for proposed and ongoing studies in RMP part IV

Not applicable.

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Not applicable.