European Union Risk Management Plan (EU-RMP)
EPREX® (epoetin alfa)

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for EPREX (erythropoietin alfa)

This is a summary of the risk management plan (RMP) for EPREX. The RMP details important risks of EPREX, how these risks can be minimised, and how more information will be obtained about EPREX's risks. EPREX's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how EPREX should be used.

This summary of the RMP for EPREX 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 EPREX's RMP.

I. The Medicine and What it is Used For

EPREX is authorised for use in chronic renal failure, cancer, autologous blood donation, surgery, and in the treatment of adult patients with low- or intermediate-1-risk myelodysplastic syndromes (see SmPC for the full indication). It contains erythropoietin alfa as the active substance and it is given intravenously or subcutaneously.

Further information about the evaluation of EPREX's benefits can be found in EPREX's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of EPREX, together with measures to minimise such risks and the proposed studies for learning more about EPREX'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 (eg, 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 timely action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of Important Risks and Missing Information

Important risks of EPREX are risks that need special risk management activities to further investigate or minimise 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 EPREX. 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 (eg, on the long-term use of the medicine);

List of Important Risks and Missing Information	
Important identified risks	Pure red cell aplasia
Important potential risks	Disease progression Survival impact
Missing information	None

II.B. Summary of Important Risks

Important Identified Risk: Pure Red Cell Aplasia	
Evidence for linking the risk to the medicine	Pure red cell aplasia was initially identified in the post-marketing setting and is also described in completed clinical trials and are also described in the current prescribing information for EPREX.
Risk factors and risk groups	*Chronic Renal Failure* Pure red cell aplasia has been reported in patients with CRF who were receiving epoetin alfa by SC administration. Risk factors for Ab-mediated PRCA can be related to both patient and product (erythropoietin). Patient-related factors associated with developing Ab-mediated PRCA include skin reactions, immune status, and treatment history. Product-related factors that could impact immunogenicity include sequence variations in proteins, degree and nature of protein glycosylation, manufacturing process, handling and storage, and components and properties of the product formulation. In addition to these, a more recent review of Ab-mediated PRCA in CKD patients receiving ESAs included genetic background, age, sex, comorbidities, and concomitant medications as additional patient-related factors, while product-related factors also included leachates and Tungsten-induced

	aggregation in addition to treatment duration and route of administration. *Cancer* Risk factors for developing PRCA and patients with cancer are not detailed in the literature. *Surgery* Risk factors for developing PRCA and patients undergoing orthopaedic surgery are not detailed in the literature.
Risk minimisation measures	Routine risk measures: SmPC Section 4.3 SmPC Section 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Monitor haemoglobin levels closely (SmPC Section 4.4) Additional risk minimisation measures: None
Important Potential Risk: Disease Progression	
Evidence for linking the risk to the medicine	Cases of disease progression have been reported in completed clinical trials and are also described in the current prescribing information for EPREX.
Risk factors and risk groups	Risk factors of disease progression depend on the type of cancer. Disease progression in oncology patients can depend on environmental and physiological factors.
Risk minimisation measures	Routine risk measures: SmPC Section 4.4 SmPC Section 5.1 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Monitor haemoglobin levels closely (SmPC Section 4.4) Additional risk minimization measures: None
Important Potential Risk: Survival Impact	
Evidence for linking the risk to the medicine	Survival data were not routinely collected in all trials for all indications. Increased mortality was observed in some cancer and chronic renal failure trials.
Risk factors and risk groups	Survival data were not routinely collected in all trials for all indications. Increased mortality was observed in some cancer and CRF trials. However, survival in patients with cancer mainly depends on the underlying tumour type and patients in different cancer trials had very different tumour types.

Risk minimisation measures	Routine risk measures: SmPC Section 4.4 SmPC Section 5.1 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Additional risk minimization measures: None

II.C. Post-authorisation Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of EPREX.

II.C.2. Other Studies in Post-authorisation Development Plan

There are no studies required for EPREX.