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

Active substance(s) (INN or common name):	Epoetin alfa
Pharmaco-therapeutic group (ATC Code):	Other antianemic preparations B03XA01
Name of Marketing Authorisation Holder or Applicant:	Janssen-Cilag Pharma GmbH, Austria JANSSEN-CILAG GmbH, Germany Janssen-Cilag NV, Belgium Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag International NV, Cyprus Janssen-Cilag s.r.o., Czech Republic Janssen-Cilag A/S, Denmark Janssen-Cilag OY, Finland JANSSEN-CILAG, France Janssen-Cilag Pharmaceutical S.A.C.I., Greece Janssen-Cilag Limited Janssen-Cilag SpA, Italy Janssen-Cilag, NV, Luxembourg Janssen-Cilag International NV, Malta Janssen-Cilag BV, Netherlands Janssen-Cilag AS, Norway Janssen-Cilag Farmaceutica, Lda, Portugal Janssen-Cilag S.A. Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag S.A., Spain Janssen-Cilag AB, Sweden Janssen-Cilag Ltd, United Kingdom
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand names):	EPREX ERYPO ERYPO FS

Data lock point for current RMP	20 December 2017	Version number	5.4
Date of final sign off	19 June 2018		

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Document No.: EDMS-ERI-13292852:1.0

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European Union Risk Management Plan (EU-RMP)
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PRODUCTS OVERVIEW

Administrative Information on the RMP

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	SII	Nonclinical Part of the Safety Specification	14 May 2018	5.3
	SIII	Clinical Trial Exposure	14 May 2018	5.3
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[1] Version 5.2 was submitted on March 30, 2018 within procedure FR/H/003/09-10,13-14/II/132/G and is therefore the most recently submitted version. However, RMP version 5.3 (current) supersedes version 5.1 as base document within procedure FR/H/003/09-10,13-14/II/129.

PRODUCTS OVERVIEW

Administrative Information on the RMP

PART	MODULE/ANNEX		Date when the module or part was last submitted (final sign off date)	Version number of RMP when last submitted[1]
	ANNEX 3	Worldwide Marketing Authorisation Status by Country (including EEA)	14 May 2018	5.3
	ANNEX 4	Synopsis of the Ongoing and Completed Clinical Trial Programme	14 May 2018	5.3
	ANNEX 5	Synopsis of the Ongoing and Completed Pharmacoepidemiological Study Programme	Not applicable	--
	ANNEX 6	Protocols for Proposed and Ongoing Trials/Studies in Categories 1-3	14 May 2018	5.3
	ANNEX 7	Specific Adverse Event Follow-up Forms	Not applicable	--
	ANNEX 8	Protocols for Proposed and Ongoing Studies in RMP Part IV	Not applicable	--
	ANNEX 9	Synopsis of Newly Available Study Reports for RMP Parts III-IV	14 May 2018	5.3
	ANNEX 10	Details of Proposed Additional Risk Minimisation Activities	Not applicable	--
	ANNEX 11	Mock up of Proposed Additional Risk Minimisation Measures	Not applicable	--
	ANNEX 12	Other Supporting Data	14 May 2018	5.3

QPPV Name(s):	PharmD, Ph.D
QPPV Signature:	Electronic signature appended at the end of this document
Contact person for this RMP:	DVM, PhD EMEA Regulatory Affairs Liaison Established Products, Global Regulatory Affairs
E-mail address or telephone number of contact person:	

Overview of Versions:

Version number of last agreed RMP:

Version number	5.0
Agreed within	Mutual Recognition Procedure FR/H/003/09-10,13-14/II/124

Current RMP Versions Under Evaluation:

RMP Version 5.2 – submitted 30 MAR 2018 – FR/H/003/09-10,13-14/II/132/G

Invented name(s) of the medicinal product in the European Economic Area (EEA)	EPREX®/ERYPO®
Authorisation procedure	Mutual Recognition and National
Brief description of product including	
Chemical class	
Summary of mode of action	Erythropoietin is a mitosis-stimulating factor and differentiating hormone, which stimulates erythropoiesis. Epoetin alfa is produced in Chinese hamster ovary cells by recombinant DNA technology and cannot be distinguished from human erythropoietin with regard to its biological properties. The efficacy of epoetin alfa has been demonstrated in humans in clinical trials and postauthorisation use. After administration of epoetin alfa, the number of erythrocytes, haemoglobin (HGB) values, reticulocyte counts, and the iron-incorporation rate increase.
Important information about its composition (eg, origin of active substance of biologicals, relevant adjuvants or residues for vaccines)	
Indication(s) in the EEA	
Current	**<u>Chronic Renal Failure</u>** EPREX, ERYPO is indicated for the treatment of symptomatic anaemia associated with chronic renal failure (CRF): • In adults and paediatrics aged 1 to 18 years on haemodialysis and adult patients on peritoneal dialysis. • In adults with renal insufficiency not yet undergoing dialysis for the treatment of severe anaemia of renal origin accompanied by clinical symptoms in patients. **<u>Cancer</u>** EPREX, ERYPO is indicated in adults receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status (eg, cardiovascular status, pre-existing anaemia at the start of chemotherapy) for the treatment of anaemia and reduction of transfusion requirements. **<u>Autologous Blood Donation</u>** EPREX/ERYPO is indicated in adults in a predonation programme to increase the yield of autologous blood. Treatment should only be given to patients with moderate anaemia (HGB concentration range between 10 to 13 g/dL [6.2 to 8.1 mmol/L], no iron deficiency) if blood-saving procedures are not available or insufficient when the scheduled major elective surgery requires a large volume of blood (4 or more units of blood for females or 5 or more units for males).

	Surgery EPREX, ERYPO is indicated for non-iron deficient adults prior to major elective orthopaedic surgery, having a high perceived risk for transfusion complications to reduce exposure to allogeneic blood transfusions. Use should be restricted to patients with moderate anaemia (eg, HGB concentration range between 10 to 13 g/dL) who do not have an autologous predonation programme available and with expected moderate blood loss (900 to 1,800 mL). **Treatment of adult patients with low- or intermediate-1-risk myelodysplastic syndromes** EPREX, ERYPO is indicated for the treatment of anaemia (HGB concentration of ≤10 g/dL) in adults with low- or intermediate-1-risk myelodysplastic syndromes (MDS).
Proposed	None.
Posology and route of administration in the EEA	
Current	**Treatment of symptomatic anaemia in adult chronic renal failure patients:** Anaemia symptoms and sequelae may vary with age, gender, and comorbid medical conditions; a physician's evaluation of the individual patient's clinical course and condition is necessary. The recommended desired HGB concentration range is between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L). EPREX, ERYPO should be administered in order to increase HGB to not greater than 12 g/dL (7.5 mmol/L). A rise in HGB of greater than 2 g/dL (1.25 mmol/L) over a 4-week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided. Due to intra-patient variability, occasional individual HGB values for a patient above and below the desired HGB concentration range may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the HGB concentration range of 10g/dL (6.2 mmol/L) to 12g/dL (7.5 mmol/L). A sustained HGB level of greater than 12g/dL (7.5 mmol/L) should be avoided. If the HGB is rising by more than 2 g/dL (1.25 mmol/L) per month, or if the sustained HGB exceeds 12g/dL (7.5 mmol/L), reduce the EPREX, ERYPO dose by 25%. If the HGB exceeds

13 g/dL (8.1 mmol/L), discontinue therapy until it falls below 12 g/dL (7.5 mmol/L) and then reinstitute EPREX, ERYPO therapy at a dose 25% below the previous dose.

Patients should be monitored closely to ensure that the lowest approved effective dose of EPREX, ERYPO is used to provide adequate control of anaemia and of the symptoms of anaemia, whilst maintaining a HGB concentration below or at 12 g/dL (7.5 mmol/L).

Caution should be exercised with escalation of erythropoiesis-stimulating agent (ESA) doses in patients with CRF. In patients with a poor HGB response to ESA, alternative explanations for the poor response should be considered.

Treatment with EPREX, ERYPO is divided into 2 stages – correction and maintenance phase.

Adult haemodialysis patients

In patients on haemodialysis where intravenous (IV) access is readily available, administration by the IV route is preferable.

Correction phase:

The starting dose is 50 international units (IU)/kg, 3 times per week.

If necessary, increase or decrease the dose by 25 IU/kg (3 times per week) until the desired HGB concentration range between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L) is achieved (this should be done in steps of at least 4 weeks).

Maintenance phase:

The recommended total weekly dose is between 75 IU/kg and 300 IU/kg.

Appropriate adjustment of the dose should be made in order to maintain HGB values within the desired concentration range between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L).

Patients with very low initial HGB (<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 IV access is not readily available EPREX, ERYPO 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 4 weeks).

Maintenance phase:

During the maintenance phase, EPREX, ERYPO can be administered either 3 times per week, and in the case of subcutaneous (SC) administration, once weekly or once every 2 weeks.

Appropriate adjustment of dose and dose intervals should be made in order to maintain HGB values at the desired level: HGB 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 IV access is not readily available, EPREX, ERYPO 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 HGB 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 anaemia:

Anaemia 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.

EPREX, ERYPO should be administered to patients with anaemia (eg, HGB concentration ≤10 g/dL [6.2 mmol/L]).

The initial dose is 150 IU/kg subcutaneously, 3 times per week.

Alternatively, EPREX, ERYPO 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 HGB 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 HGB concentrations for a patient above and below the desired HGB concentration range may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the desired HGB concentration range between 10g/dL (6.2 mmol/L) to 12g/dL (7.5 mmol/L). A sustained HGB concentration of greater than 12g/dL (7.5 mmol/L) should be avoided; guidance for appropriate dose adjustment for when HGB concentrations exceed 12g/dL (7.5 mmol/L) is described below.

If the HGB 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 (QW).

If the HGB 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 HGB 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 HGB 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 HGB concentrations between 10 g/dL to 12 g/dL

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

If the HGB concentration exceeds 13 g/dL (8.1 mmol/L), discontinue therapy until it falls below 12 g/dL (7.5 mmol/L) and then reinstitute EPREX, ERYPO therapy at a dose 25% below the previous dose.

Patients should be monitored closely to ensure that the lowest approved dose of ESA is used to provide adequate control of the symptoms of anaemia.

EPREX, ERYPO therapy should continue until 1 month after the end of chemotherapy.

Treatment of adult surgery patients in an autologous blood donation programme:

Mildly anaemic patients (haematocrit [HCT] of 33% to 39%) requiring predeposit of ≥4 units of blood should be treated with EPREX, ERYPO 600 IU/kg intravenously, 2 times per week for 3 weeks prior to surgery. EPREX, ERYPO should be administered after the completion of the blood donation procedure.

Treatment of adult patients scheduled for major elective orthopaedic surgery:

The recommended dose is EPREX, ERYPO 600 IU/kg administered subcutaneously weekly for 3 weeks (Days -21, -14, and -7) prior to surgery and on the day of surgery.

In cases where there is a medical need to shorten the lead time before surgery to less than 3 weeks, EPREX, ERYPO 300 IU/kg should be administered subcutaneously daily for 10 consecutive days prior to surgery, on the day of surgery, and for 4 days immediately thereafter.

If the HGB level reaches 15 g/dL, or higher, during the perioperative period, administration of EPREX, ERYPO should be stopped and further dosages should not be administered.

Paediatric population

Treatment of symptomatic anaemia in chronic renal failure patients on haemodialysis

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

In paediatric patients, the recommended HGB concentration range is between 9.5 g/dL to 11 g/dL (5.9 to 6.8 mmol/L). EPREX, ERYPO should be administered in order to increase HGB to not greater than 11 g/dL (6.8 mmol/L). A rise in HGB of greater than 2 g/dL (1.25 mmol/L) over a 4-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 EPREX, ERYPO is used to provide adequate control of anaemia and of the symptoms of anaemia.

Treatment with EPREX, ERYPO is divided into 2 stages – correction and maintenance phase.

In paediatric patients on haemodialysis where IV access is readily available, administration by the IV 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 HGB 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 4 weeks).

Maintenance phase:

Appropriate adjustment of the dose should be made in order to maintain HGB 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. Paediatric patients with very low initial HGB (<6.8 g/dL or <4.25 mmol/L) may require higher maintenance doses than patients whose initial HGB is higher (>6.8 g/dL or >4.25 mmol/L).

Treatment of paediatric patients with chemotherapy-induced anaemia

The safety and efficacy of EPREX, ERYPO in paediatric patients receiving chemotherapy have not been established

Treatment of paediatric surgery patients in an autologous predonation programme

The safety and efficacy of EPREX, ERYPO in paediatrics have not been established. No data are available.

Treatment of paediatric patients scheduled for major elective orthopaedic surgery

The safety and efficacy of EPREX, ERYPO in paediatrics 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 EPREX, ERYPO syringe to stand until it reaches room temperature. This usually takes between 15 and 30 minutes.

Treatment of symptomatic anaemia in adult chronic renal failure patients

In patients with CRF where IV access is routinely available (haemodialysis patients), administration of EPREX, ERYPO by the IV route is preferable.

Where IV access is not readily available (patients not yet undergoing dialysis and peritoneal dialysis patients), EPREX, ERYPO may be administered as a SC injection.

Treatment of adult patients with chemotherapy-induced anaemia

EPREX, ERYPO should be administered as a SC injection.

Treatment of adult surgery patients in an autologous predonation programme

EPREX, ERYPO should be administered by the IV route.

Treatment of adult patients scheduled for major elective orthopaedic surgery

EPREX, ERYPO should be administered as a SC injection.

Treatment of symptomatic anaemia in paediatric chronic renal failure patients on haemodialysis

In paediatric patients with CRF where IV access is routinely available (haemodialysis patients), administration of EPREX, ERYPO by the IV route is preferable.

Intravenous administration

Administer over at least 1 to 5 minutes, depending on the total dose. In haemodialysed 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 EPREX, ERYPO by IV infusion or in conjunction with other drug solutions.

Subcutaneous administration

A maximum volume of 1 mL at 1 injection site should generally not be exceeded. In case of larger volumes, more than 1 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 EPREX, ERYPO subcutaneously themselves, instruction as to the proper dosage and administration should be provided. As with any injectable product, check that there are no particles in the solution or change in colour. **Treatment of adult patients with low- or intermediate-1-risk MDS** EPREX, ERYPO should be administered to patients with anaemia (eg, HGB concentration ≤10 g/dL [6.2 mmol/L]). The recommended starting dose is EPREX, ERYPO 450 IU/kg (maximum total dose is 40,000 IU) administered subcutaneously once every week. It is recommended that response be assessed at Week 8. If no erythroid response is achieved after 8 weeks according to International Working Group 2006 criteria, and the HGB concentration is below 11 g/dL (6.8 mmol/L), the dose should be increased from 450 IU/kg once every week to 1,050 IU/kg once every week (maximum dose is 80,000 IU per week). Appropriate dose adjustments should be made to maintain HGB concentrations within the target range of 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L). Epoetin alfa should be withheld or the dose reduced when the HGB concentration exceeds 12 g/dL (7.5 mmol/L). Upon dose reduction, if HGB concentration drops ≥1 g/dL, the dose should be increased. A sustained HGB concentration of greater than 12 g/dL (7.5 mmol/L) should be avoided. EPREX, ERYPO should be administered as a SC injection.
Proposed	None
Pharmaceutical form(s) and strength(s)	
Current	Clear, colourless solution for injection in prefilled syringe in the following strengths: 2,000 IU/mL, 4,000 IU/mL, 10,000 IU/mL, and 40,000/mL. EPREX is available in the following prefilled syringe volumes: 1,000 IU in 0.5 mL, 2,000 IU in 0.5 mL,

	3,000 IU in 0.3 mL, 4,000 IU in 0.4 mL, 5,000 IU in 0.5 mL, 6,000 IU in 0.6 mL, 8,000 IU in 0.8 mL, 10,000 IU in 1.0 mL, 20,000 IU in 0.5 mL, 30,000 IU in 0.75 mL, and 40,000 IU in 1.0 mL.

Country and date of first authorisation worldwide	**Switzerland**	**27 July 1988**
Country and date of first launch worldwide	Portugal, Malta	November 1988
Country and date of first authorisation in the EEA	France	4 August 1988

Is the product subject of additional monitoring in the EU? ☐ **Yes** ☑ **No**

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

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population

Active substance	Epoetin alfa
Product(s) concerned	EPREX ERYPO ERYPO FS
MAH/MAA name	Janssen-Cilag Pharma GmbH, Austria JANSSEN-CILAG GmbH, Germany Janssen-Cilag NV, Belgium Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag International NV, Cyprus Janssen-Cilag s.r.o., Czech Republic Janssen-Cilag A/S, Denmark Janssen-Cilag OY, Finland JANSSEN-CILAG, France Janssen-Cilag Pharmaceutical S.A.C.I., Greece Janssen-Cilag Limited Janssen-Cilag SpA, Italy Janssen-Cilag, NV, Luxembourg Janssen-Cilag International NV, Malta Janssen-Cilag BV, Netherlands Janssen-Cilag AS, Norway Janssen-Cilag Farmaceutica, Lda, Portugal Janssen-Cilag S.A. Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag S.A., Spain Janssen-Cilag AB, Sweden Janssen-Cilag Ltd, United Kingdom

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Indication

EPREX, ERYPO (epoetin alfa) is indicated in the European Union (EU)

- For the treatment of symptomatic anaemia associated with CRF
  - In adults and paediatrics aged 1 to 18 years on haemodialysis and adult patients on peritoneal dialysis.
  - In adults with renal insufficiency not yet undergoing dialysis for the treatment of severe anaemia of renal origin accompanied by clinical symptoms in patients.
- In adults receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status (eg, cardiovascular status, pre-existing anaemia at the start of chemotherapy) for the treatment of anaemia and reduction of transfusion requirements.
- In adults in a predonation programme to increase the yield of autologous blood. Treatment should only be given to patients with moderate anaemia (HGB concentration range between10 to 13 g/dL [6.2 to 8.1 mmol/L], no iron deficiency) if blood-saving procedures are not available or insufficient when the scheduled major elective surgery requires a large volume of blood (4 or more units of blood for females or 5 or more units for males).
- For non-iron-deficient adults prior to major elective orthopaedic surgery, having a high perceived risk for transfusion complications to reduce exposure to allogeneic blood transfusions. Use should be restricted to patients with moderate anaemia (eg, HGB concentration range between 10 to 13 g/dL [6.2 to 8.1 mmol/L]) who do not have an autologous predonation programme available and with expected moderate blood loss (900 to 1,800 mL).

The current EPREX Summary of Product Characteristics (SmPC) was approved by L'Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) in her capacity as the Reference Member State in the Mutual Recognition Procedure in July 2015 and the information in this document reflects the current labelling.

In addition to the current indications as noted above, an indication for the treatment of adult patients with low- or intermediate-1-risk MDS has been proposed and approved: EPREX, ERYPO is indicated for the treatment of anaemia (HGB concentration of ≤10 g/dL) in adults with low- or intermediate-1-risk MDS.

Of note, the term "Surgery" used throughout this document relates to the indication associated with the treatment of non-iron-deficient adults prior to major elective orthopaedic surgery.

This risk management plan (RMP) includes safety data from patients receiving EPREX as well as relevant safety data for other ESAs including PROCRIT®, where appropriate, to provide a comprehensive characterisation of identified and potential safety risks.

SI.1. Epidemiology of the Disease

Chronic Renal Failure

Incidence and Prevalence

Adults

The National Health Service (NHS) in the United Kingdom provided annual data on primary care activity through the Quality and Outcomes Framework for all NHS hospitals through NHS Reference Costs. Adjustments for mortality suggest that approximately 119,000 new cases of chronic kidney disease (CKD) were diagnosed in 2009 (Kerr 2012). A study conducted in France estimated the annual incidence rate (IR) of CKD Stage 3 to 5, (defined as estimated glomerular filtration rate [eGFR]<60 mL/min per 1.73m^2) at 977.7 per million inhabitants (Ayav 2016). In the United States, the adjusted IR of end-stage renal disease (ESRD) in 2015 was estimated to be 357/million/year (United States Renal Data System 2017).

A recent review of population studies of CKD conducted in Europe reported the age-adjusted prevalence of CKD Stage 3 to 5 ranged from 1.0% (95% confidence interval [CI]: 0.7-1.3) in Italy to 5.9% (95% CI: 5.2-6.6) in Germany for people aged 20 to 74 years. For Stages 1 to 5, the prevalence ranged from 3.3% (3.3-3.3) in Norway to 19.4% (18.1-20.7) in Germany (Bruck 2016). In a nationally representative population-based study in Portugal, the overall prevalence of CKD was 6.1% and the prevalence was 5.6%, 0.3%, and 0.18% for Stages 3, 4, and 5, respectively (Vinhas 2011). Data from a representative sample of 743,935 adults in England in 2010 observed that a 21.2% of the total General Practice Research Database population, or approximately 600,000 people, had a classification of mildly impaired eGFR, and for Stages 3 to 5 the prevalence was 5.9% (165,942). The most common stage reported was 3a at 4.0% (Jameson 2014). In Italy, a crude prevalence rate of 7.05% (95% CI: 6.48-7.65) was calculated based on a total sample of 8,693 people aged 35 to 79 (De Nicola 2015). A similar prevalence (approximately 7%) was observed in a population-based study in Romania (Cepoi 2012). The same study observed the prevalence of Stage 3a CKD to be approximately 6% and the prevalence of Stages 3b, 4, and 5 CKD combined to be approximately 1%. According to the 2007 to 2012 National Health and Nutrition Examination Survey (NHANES) in the United States, the prevalence of CKD in adults aged 20 and over was 13.6%. Among these, the prevalence rate for Stage 3 CKD was approximately 6% (Saran 2015a).

End-stage Renal Disease

Anaemia develops early in the course of renal disease and progresses with loss of renal function (Astor 2002; Kazmi 2001). Approximately 5% of patients with an eGFR between 30 and 59 mL/min/1.73 m^2 body surface area (BSA) and 44% of patients with eGFR between 15 and 29 mL/min/1.73 m^2 BSA are anaemic (Astor 2002). In patients who have progressed to ESRD, anaemia is a ubiquitous comorbidity (United States Renal Data System [USRDS] 2010). In the United States, anaemia (defined as serum HGB levels ≤12 g/dL in women and ≤13 g/dL in men), was twice as prevalent in people with CKD (15.4%) as in the general population (7.6%). The prevalence of anaemia increased with stage of CKD, from 8.4% at Stage 1 to 53.4% at Stage 5.

A total of 22.8% of CKD patients with anaemia reported being treated for anaemia within the previous 3 months: 14.6% of patients at CKD Stages 1 to 2 and 26.4% of patients at Stages 3 to 4 (Stauffer 2014).

Children

Several paediatric nephrology societies from European countries have provided data on the early stages of CKD, including the European Society for Paediatric Nephrology and the European Renal Association and European Dialysis and Transplantation Association (ERA-EDTA). Between 2009 and 2011, in 37 European countries, a total of 1,697 patients aged 0 to 14 years started renal replacement therapy (RRT). The average overall IR of paediatric RRT was 5.5 per million of the age-related population (pmarp). In 9 countries that collected data from paediatric and adult centres in a registry, the IR was 8.3 pmarp for children aged 0 to 19 years and 13.3 for children aged 15 to 19 years (Chesnave 2014). This registry reported that for patients where complete data was available, 21.3% of patients had subtarget HGB levels, using the United Kingdom (UK)-NICE (National Institute for Health and Care Excellence) guidelines of a target HGB of 10.0 to 12.0 g/dL (Krischock 2016). In every registry examined in a review of the literature, the incidence of RRT was twice as high in the United States as in Western Europe in the 15- to 19-year-old age group (30.6 versus 15.3) and was higher in the 0- to 14-year-old age group (10.5 versus 6.5 in Western Europe). This difference might be partly explained by the timing of initiation of RRT (Harambat 2012).

At the end of 2011, there were 3,595 RRT patients aged 14 years and under in 37 European countries, resulting in a point prevalence rate of 27.9 pmarp. Prevalence varies significantly among these countries with an interquartile range of 21.8 to 43.9 pmarp. In the 9 countries that collected data from paediatric and adult centres, the prevalence rate was 58.0 pmarp for children aged 0 to 19 years and 109.0 for children aged 15 to 19 years (Chesnaye 2014). In 2012 in the United States, 7,522 children (<19 years old) had prevalent ESRD, which represents a 1.3% decrease from the previous year (Saran 2015b).

In the United States, anaemia has been described as a universal problem among children with CRF (Koshy 2008). This contrasts with McClellan's observation that approximately half of adults with CRF have anaemia (McClellan 2002; McClellan 2004). Among children, as among adults, the prevalence of anaemia increases with the severity of CRF. For instance, among patients ages 2 years and older in the North American Paediatric Renal Trials and Collaborative Studies (NAPRTCS) database, the prevalence of anaemia increased from 18.5% in Stage 2 CRF to 68% in Stage 5 CRF (Staples 2009).

Among paediatric patients with CRF, anaemia, (defined here as a HGB concentration <12 g/dL or treatment with iron or darbepoetin alfa) was observed in a Canadian study in 31% of patients with Stage 1 disease and 93% of those with Stage 4 or 5 disease (Wong 2006). Ardissino suggests that paediatric CRF usually progresses to ESRD by age 20 (up to 68% of patients overall) (Ardissino 2003). Therefore, it is likely that nearly all paediatric patients, other than those with mild CRF, will at some point develop anaemia, either as they progress toward ESRD, or at an earlier stage of the disease.

Demographics of the Target Population

Adults

In a review of studies on the prevalence of CKD Stages 3 to 5 in adults in Europe, the lowest rate was in those aged 20–44 years, and increased with age (Bruck 2016). According to data from a sub-sample of almost 10,000 adults in the United States (US) NHANES 2001-2010, those with CRF were older (mean age, 64.2 years) than those without (Kuznik 2013). For ESRD in the United States in 2012, the adjusted prevalence per million was 83 for ages 0 to 19 years, 938 for ages 20 to 44 years, 3,550 for ages 45 to 64 years, 6,302 for ages 65 to 74 years, and 6,261 for ages 75+ years (Saran 2015b).

In the United Kingdom in 2010, 92.9% of patients with Stage 3 to 5 CKD were over 60 years of age, and only 0.5% were between the ages of 18 and 39 (Jameson 2014).

An Italian study of adults between the ages of 35 and 79 years observed a crude prevalence rate for all CKD patients to be 2.65% (2.05-3.34) for ages 35 to 49 years, 3.41% (2.61-4.37) for ages 50 to 59 years, 8.71% (7.44-10.11) for ages 60 to 69 years, and 16.97% (15.09-18.99) for ages 70 to 79 years (De Nicola 2015).

Sex

In a large nationally representative sample from the United Kingdom, the prevalence of CKD was higher in women than men, 47.5% of all identified CKD patients were men (Jameson 2014). Similar findings are observed in the US NHANES 2001-2010, where 58% of those with CRF were women (Kuznik 2013). However, men with CRF are 50% more likely than women to progress to ESRD (CDC 2010).

In contrast, an Italian study observed a slightly higher crude prevalence rate for men (7.54% [6.72-8.42]) compared with women (6.54% [5.76-7.38]) for all CKD patients. For Stage 5 disease, the crude prevalence rate was 0.13% (0.04-0.30) for men and 0.11% (0.03-0.28) for women (De Nicola 2015). A systematic review of the literature reported that male patients showed a higher hazard ratio (HR) for progression to ESRD than women, (HR 1.37, 95% CI: 1.17–1.62), (Tsai 2016).

Race

In the most recent USRDS using NHANES data from 2007 to 2012, the prevalence of all CKD was 13.9% for non-Hispanic Whites, 15.9% for non-Hispanic Blacks, and 11.7% for Other (Saran 2015a). Based on statistics provided by the National Kidney Disease Education Program (NKDEP) in the United States, compared with Whites, African Americans have 3.8 times higher risk for kidney failure, Native Americans 2 times higher, and Asians 1.3 times higher (NKDEP 2011).

In the Prevalence of Anaemia in Early Renal Insufficiency study (McClellan 2004), 2 thresholds for anaemia were defined; the first at a HGB concentration of ≤12 g/dL and the other at a HGB concentration of ≤10 g/dL. The study demonstrated that, relative to Caucasian patients, the odds

ratios (ORs) for having anaemia at these respective thresholds among African-American patients with CRF were 1.6 and 2.0, respectively, and among Hispanic patients with CRF, the ORs were 1.5 and 1.6, respectively.

Children

Sex

A consistent finding in Europe is that there is a predominance of male children who have CKD (male/female ratio ranging from 1.3 to 2.0) reflecting, in particular, the higher incidence of congenital anomalies of the kidney and urinary tract in boys than girls (Harambat 2012). Males account for 55% of adolescents with ESRD, and have been found to have a slightly higher IR (24.1 per million) than females (21.0 per million) (Ferris 2006).

Race

Among adolescents with ESRD, those from minority backgrounds have the highest incidence of ESRD. Rates by ethnicity are as follows: African American, 41.0 per million; Native American, 26.2 per million; Asian/Pacific Islanders, 24.9 per million; and Whites, 18.8 per million (Ferris 2006). Furthermore, focal segmental glomerulosclerosis, the main cause of glomerular disease, is especially common among Black adolescents (NAPRTCS 2008).

In the United Kingdom, in 2008, the prevalence and incidence of RRT in children from the South Asian population were 2.5 and 1.5 times greater, respectively, than that of the White population aged 1 to 15 years old (Harambat 2012).

Risk Factors for the Disease

Initiating factors that play a role in starting the cycle of nephron loss, include older age, male sex, diabetes, and perpetuating factors that drive the disease process onward, include proteinuria, hypertension, or hyperuricaemia (Tsai 2016). Other risk factors include automimmune diseases, systemic infections, urinary tract infections, nephrolithiasis, lower urinary tract obstruction, hyperuricaemia, acute kidney injury, and a family history of the disease. Sociodemographic factors that increase the risk of CKD include older age, black race, smoking, heavy alcohol use and obesity (Drawz 2015). According to data from the United Kingdom (UK) Renal Registry, the prevalence of RRT was also higher in socially deprived areas of the United Kingdom.

Currently, diabetes mellitus is the most common cause of RRT for ESRD affecting more than 22% of the incident patients (Harambat 2012).

Main Treatment Options

Chronic kidney disease has no cure, but depending on the underlying cause, some types can be treated. Treatment consists of measures to help control signs and symptoms of CKD, reduce complications, and slow the progression of the disease. Kidney failure complications can be controlled to make the patient more comfortable and include angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers to preserve kidney function and lower blood pressure, statins to lower cholesterol, erythropoietin supplements to induce production of more

red blood cells (RBCs), in which loss is associated with anaemia, diuretics to maintain balance of fluids in the body, and calcium and vitamin D supplements. Treatment for patients with ESRD requires dialysis or a kidney transplant (Mayo Clinic 2015, chronic kidney failure).

Mortality and Morbidity

Adults

In a large retrospective study among patients with incident CRF in a health maintenance organisation in the United States, patients with the most severe anaemia (HGB <10.5 g/dL) had more than a 5-fold increased risk of mortality (HR=5.27; 95% CI: 4.37-6.35) compared with patients who were not anaemic (Thorp 2009). Anaemia has been shown to be an independent predictor for increased coronary heart disease mortality and all-cause mortality in patients with CRF (Astor 2006). Among patients with ESRD, cardiovascular disease (CVD) accounts for more than half of all deaths, and after a hospitalisation for congestive heart failure (CHF), carries a 2-year mortality of 58% among patients with ESRD (Collins 2003). Conversely, among patients with CHF who were admitted to community hospitals, the relative risk (RR) of mortality in the year after hospitalisation for those with CRF compared with those without CRF was 1.4 (95% CI: 1.2, 1.8) and RR for anaemia (relative to those without anaemia) was 1.6 (95% CI: 1.2, 2.2). Relative risk for both CRF and anaemia together relative to those with neither was 2.2 (95% CI: 1.4, 3.3) (McClellan 2002). In a large database of patients with left ventricular dysfunction, lower values of glomerular filtration rate (GFR) and lower HCT values were associated with increased mortality, and the 2 together were associated with greater mortality than would be predicted by both factors acting independently (Al-Ahmad 2001). In contrast, the results of a clinical trial (Pfeffer 2009), described in the following paragraph, suggested that correction of anaemia in patients with CRF, to a target HGB of 13 g/dL, did not reduce mortality (Pfeffer 2009).

In a UK prospective cohort study of people with CKD, the mortality rate was 6.5% per year (Landray 2010). A meta-analysis has demonstrated that the risk of mortality in CRF rises exponentially with decreasing GFR. Mortality in ESRD patients is very high. Five-year mortality rates in incidence in patients with RRT are 52% (all patients), 32% (for those 15 to 64 years of age), and 73% (for those over 65 years of age). Five-year mortality in patients on dialysis is almost 5 times as high as that after kidney transplantation: 60% and 13%, respectively. Mortality is lower in Europe compared with the United States (Zoccali 2009).

For the year 2012, in the United States the 5-year survival probability for ESRD patients initiating treatment was 87.0% for children 19 years and younger, 73.0% for ages 20 to 44 years, 53.3% for ages 45 to 64 years, 33.0% for ages 65 to 74 years, and 15.8% for ages 75+ years (Saran 2015b).

Children

The mortality rate in children with RRT is about 30 times higher than in their healthy peers. Infants with severe renal disease are at higher risk of death in the first 2 years of life, but outcomes thereafter are comparable to those of older children. The 2 major causes of mortality in

paediatric patients with RRT are CVD and infections, accounting for 30% to 40% and 20% to 50% of deaths, respectively. Also, the burden of morbidity from CVD and infection is high, as, for example, infections cause 600 admissions per 1,000 person years (PY) in the first month of starting dialysis according to the most recent USRDS report (Harambat 2012).

In Europe, for the 37 countries that report to the European Society for Paediatric Nephrology, European Renal Association (ERA), and European Dialysis and Transplantation Association (EDTA) registries, for children on RRT, the overall 4-year survival rate for ages <19 years was 93.7% for 2007 to 2011, while for ages 0 to 4 years it was 87.1%, for ages 5 to 9 years it was 95.3%, for ages 10 to 14 years it was 96.2%, and for ages 15 to 19 years it was 96.3% (Chesnaye 2014). In the United States from 2007 to 2011, the 1-year all-cause mortality rate (per 1,000) for children with ESRD was 85 for ages 0 to 4 years, 39 for ages 5 to 9 years, 11 for ages 10 to 14 years, and 23 for ages 15 to 19 years. This represents an overall decrease of 22.2% compared with 2002 to 2006 (Saran 2015b)

Cancer

Incidence and Prevalence

A review summarised that anaemia is a frequent finding in cancer patients and occurs in more than 40% of cases, with the incidence rising to 90% in patients treated with chemotherapy (Dicato 2010). However, another review observed that anaemia prevalence was dependent on the definition of anaemia; for example, 7% of patients with Hodgkin's disease had anaemia when the condition was defined as a HGB level <90.0 g/L while as many as 86% of patients had anaemia when it was defined as a HGB value <110 g/L. Prevalence also varied by cancer type and disease state; 40% of patients with early-stage colon tumours and nearly 80% of patients with advanced disease had anaemia (Knight 2004).

The European Cancer Anaemia Survey (ECAS) (Ludwig 2004) was conducted to document the prevalence, incidence, evolution, severity, and management of anaemia in a large, representative population of European patients with cancer. It was a prospective, epidemiologic, observational survey conducted in 748 centres in 24 European countries. It defined anaemia as HGB <12.0 g/dL, with the following subclassifications based on HGB concentration: HGB 10.0 to 11.9 g/dL (mild), 8.0 to 9.9 g/dL (moderate), and <8.0 g/dL (severe). The ECAS also indicated that the severity of anaemia increased with the number of cycles of chemotherapy and varied according to cancer type and therapy. Reports from the ECAS estimate the incidence of anaemia to be 59.8% for patients with breast cancer and 74.8% for patients with gynaecologic cancer, while 62.4% of patients with breast cancer and 81.4% of patients with gynaecologic cancer were anaemic at some time during the survey. Similarly, 83.3% of patients with lung cancer who received chemotherapy were anaemic at some time during the survey (Barrett-Lee 2005; Kosmidis 2005). Another analysis of ECAS data reported that for lymphoma and multiple myeloma patients anaemia prevalence was 72.9%, and incidence in chemotherapy patients was 55.4% (Birgegård 2006). In patients not receiving antineoplastic treatment, anaemia was present in 32%, including 25% of patients considered to be in remission (Gascon 2006). A Finnish study of patients who received chemotherapy for solid tumours, 27% had a HGB level

<12 g/dL, (Kellokumpu-Lehtinen 2011). In Germany, a study conducted in patients treated on an outpatient basis for any tumour type reported that 49.1% of the patients had HGB concentrations below 12.0 g/dL and 10.9% had concentrations below 10.0 g/dL (Link 2013). All of these studies demonstrate that anaemia affects a large proportion of cancer patients regardless of the type of tumour.

Demographics of the Target Population

Age

Anaemia occurs most often in older individuals, with its prevalence in elderly patients with cancer significantly increasing (Penninx 2007). A Spanish study reported the median age of cancer patients with anaemia was 63 years (Steegmann 2013). Based on data from the ECAS, 44% of elderly patients (>69 years) were anaemic at time of enrolment, compared with 40% of patients 60 to 69 years of age, and 36% of patients 50 to 59 years of age (Birgegård 2005). Similarly, a German study, using the same definition of anaemia (HGB levels below 12 g/dL), reported anaemia prevalence of 45.6% for those ≤65 years, and 52.8% for those >65 (Link 2013).

Sex

In the ECAS, female gender was observed to be an independent predictor of anaemia (Barrett-Lee 2006).

Risk Factors for the Disease

Risk factors for anaemia in patients with cancer could include nutritional deficiencies, major organ problems, lower initial HGB (≤12.9 g/dL in women and ≤13.4 g/dL in men), having lung or gynaecologic cancer versus gastrointestinal or colorectal cancer, treatment with platinum chemotherapy, and female gender (Barrett-Lee 2006; American Cancer Society 2014). Specifically, in patients with breast cancer, risk factors for anaemia could also include exposure to taxanes, high-dose anthracycline treatment, mastectomy, and being over 60 years of age (Chaumard 2012).

Main Treatment Options

Treatment options for treating anaemia in patients with cancer can include eating nutrient-rich foods, taking iron and folic acid supplements, blood transfusions, and drugs such as erythropoietin that help the body make its own new RBCs (American Cancer Society 2014).

Mortality and Morbidity

Anaemia may adversely affect survival in patients with cancer. In a comprehensive literature review of survival with and without anaemia, an association of anaemia with reduced survival times was observed consistently for carcinoma of the lung, cervix, head and neck, prostate, lymphoma, and multiple myeloma (Caro 2001). Similarly, survival probability for cancer patients with anaemia severity ≥Grade 2 (HGB <10.0 g/dL) was significantly lower than for patients with no anaemia (Nakamura 2011). A recent systematic review of studies on outcomes of blood transfusions for anaemia in patients with advanced cancer observed a significant

proportion of participants (23% to 35%) dying within 2 weeks of their transfusion. Overall survival for inpatients receiving transfusion was lower (35 days versus 86 days) than that for outpatients (Preston 2012).

Autologous Blood Donation

Incidence and Prevalence

The incidence of autologous blood donation (ABD) is not detailed in the literature.

The most recent data found on the prevalence of ABD comes from a questionnaire in 2000 from 43 member states of the Council of Europe. The responses indicated that predeposit ABD is not practised anywhere on a very large scale but it is moderately common (4.6% to 7.8% of allogenic blood) in Italy, Germany, France, Czech Republic, and Luxembourg. Up to 533,839 predeposit units were collected in Europe in 2000, which is equivalent to 3.3% of the allogeneic units donated in the same year. The autologous units issued in 2000 represented 85% of those collected, and those used represented 70% of those collected, although there were wide variations between countries (Politis 2004). In the United States, ABD represented 4.0% of all blood donations (Goodnough 2004). In the United States for the years 2008-2011, of the more than 3,500,000 patients who underwent elective orthopaedic surgery, 2.4% received an autologous blood transfusion (Menendez 2014).

In Spain, preoperative ABD has increased from 15,123 units in 1994 to 24,390 units in 2004 with fluctuations between years. The most common area of application of preoperative ABD was orthopaedic surgery procedures, where 80% of the collected preoperative ABD units were actually transfused (Garcia-Erce 2007). A study conducted in the United States showed that 16% of total hip arthroplasties were performed in anaemic patients (HGB <12.5 g/dL), and 76% of them had an ABD prior to surgery (Bou Monsef 2014).

Demographics of the Target Population

Few studies have discussed the demographics of ABD. One study (Martin 2010), examined all patients who donated autologous blood prior to cardiac surgery who were matched to a non-donor according to age, body weight, body mass index (BMI), sex, and other covariates. The average age of the donors was 58 years old and there were more men than women (156 versus 60, respectively). The average BMI was 26, which is considered overweight. In the United States, black and Hispanic patients receiving elective orthopaedic surgery were less likely to receive an autologous blood transfusion than white patients (Menendez 2014).

Risk Factors for the Disease

Risk factors for ABD include becoming anaemic, hypovolaemic, or having a low blood count before surgery.

Main Treatment Options

Not applicable.

Mortality and Morbidity

Autologous blood donation is a preoperative procedure and therefore literature on morbidity and mortality is scarce. The aforementioned study (Martin 2010) observed that there were no major adverse events such as myocardial infarction (MI), stroke, or death in the donor group during the preoperative ABD process. Approximately 1 in 16,783 autologous donations is associated with an adverse reaction severe enough to require hospitalisation, which is 12 times the risk associated with community donation by healthy individuals (Goodnough 2004).

Surgery

Incidence and Prevalence

Hip replacement

The rates of hip and knee replacement surgeries have increased in several European countries in the past 10 years, mostly due to the ageing population. In a study of data from 2014, Germany, Austria, Belgium, and Finland had the highest rates of hip replacement (293, 279, 247, and 245 surgeries per 100,000 population, respectively) among European countries, and Switzerland had a rate of 305/100,000 population. The overall rate of hip replacement for the EU27 (Germany, Austria, Sweden, Finland, Belgium, France, Denmark, Luxembourg, Netherlands, Slovenia, United Kingdom, Greece, Czech Republic, Italy, Hungary, Croatia, Lithuania, Ireland, Latvia, Spain, Slovak Republic, Estonia, Portugal, Poland, Malta, Romania, Cyprus) was 189 per 100,000 population (OECD/EU 2016).

Knee replacement

In the same study from 2014, Austria, Germany, Belgium, and Finland had the highest rates of knee replacement (221, 197, 191, and 190) per 100,000 population, respectively, Switzerland had a rate of 214/100,000 population. The overall rate of knee replacement for the EU25 (Austria, Finland, Germany, Belgium, Luxembourg, Denmark, Malta, Sweden, United Kingdom, France, Netherlands, Czech Republic, Slovenia, Spain, Italy, Lithuania, Portugal, Hungary, Cyprus, Croatia, Ireland, Latvia, Poland, Romania, Slovak Republic) was 130 per 100,000 population (OECD/EU 2016).

A systematic review of 19 studies on anaemia prevalence in patients undergoing major orthopaedic surgery reported preoperative anaemia to be highly prevalent, ranging from 24% among patients undergoing total hip replacement (THR) or total knee replacement (TKR) surgery to 44% among patients undergoing hip fracture surgery. Prevalence of postoperative anaemia was 51% in patients undergoing hip or knee replacement surgery (Spahn 2010) and 20.5% of THR patients had an HGB level <10g/dL on the day of discharge (Jans 2016). As mentioned above, a US study of total hip arthroplasty patients, 16% were performed in anaemic patients (HGB <12.5 g/dL) (Bou Monsef 2014). A Danish study of THR and TKR procedures reported that 12.8% of patients had preoperative anaemia (Jans 2014) and an Austrian study reported preoperative anaemia rates of 17% and 16% for THR and TKR respectively (Gombotz 2014).

Demographics of the Target Population

Hip and knee replacement surgery is mainly carried out among people aged 60 and over, for severe osteoarthritis, but it can also be performed on younger patients (OECD/EU 2016). In the United Kingdom, 1 study reported that 62.2% of THR patients were women with a mean age of 69.9 years and 37.8% were men with a mean age of 67.8 years. For TKR patients, 58.4% were women with a mean age of 70.3 years while 41.6% were men with a mean age of 69.4 years (Culliford 2015)

A systematic review of the epidemiology of hip and knee arthroplasty reported higher rates in Caucasians than in African Americans. Similar arthroplasty utilisation rates were observed in men and women in 3 studies based in the United States, Denmark, and England (Singh 2011).

Risk Factors for the Disease

The leading diagnoses for patients in the United States who underwent THR in 2003 were osteoarthritis (OA, 81%), other bone/musculoskeletal disease (9%), and fracture of the femoral neck (4%). For partial hip replacement (PHR), the most frequent diagnoses were fracture of the femoral neck (88%), pathologic fracture (3%), and other bone/musculoskeletal disease (3%). For PHR, the most frequent principal diagnoses were complication of the device, implant, or graft (89%); OA (2%); and fracture of the neck of the femur (2%). Approximately 60% of the patients treated with THR or PHR were 65 years of age or older, and most of their admissions to the hospital were planned. About 80% of the patients treated with PHR were age 75 years or older and about 80% of their admissions were emergency admissions. Thus, the epidemiology of surgery for THR together with PHR provides a reasonable approximation to the epidemiology of elective hip replacement surgery (Zhan 2008; Löfvendahl 2011). The main indication for TKR is arthritic deterioration of the joint (NIH Consensus Panel 2004; Mayo Clinic 2013, knee replacement). Therefore, most TKRs are elective.

Main Treatment Options

Not applicable.

Mortality and Morbidity

A systematic review of 32 studies published over the last decade that provided mortality data post-THR surgery estimated the pooled mortality rate to be 0.30% (95% CI: 0.22-0.38) at 30 days and 0.65% (95% CI 0.50-0.81) at 90 days following hip replacement (Berstock 2014).

A Danish study examining THR and TKR procedures reported that 12.8% of the patients had postoperative anaemia. The mortality rate of 1.1% for those with preoperative anaemia was significantly higher than the mortality rate for those who did not have anaemia (0.3%), and the mortality rate for all THR and TKR patients was 0.4% (Jans 2014). A systematic review of studies on the epidemiology of anaemia in patients undergoing major orthopaedic surgery observed both preoperative and postoperative anaemia to be associated with increased mortality in all 3 prospective studies that investigated this association. Overall ORs for death were increased 1.5- to over 2-fold in anaemic versus non-anaemic patients (Spahn 2010).

Myelodysplastic Syndromes

Incidence and Prevalence

Orphanet estimates the incidence of MDS to be 1.5/100,000 in Europe (Orphanet 2017). Similarly, the annual IR of MDS is 3.8 per 100,000 in the United Kingdom with an age standardised rate (ASR) of 2.6/100,000 according to the Haematological Malignancy Research Network (HMRN 2017), which is a collaboration between research at the University of York, a clinical network of 14 hospitals, and St. James' hospital in Leeds. In the Netherlands, the ASR was estimated to be 2.8/100,000 in 2006-2010 (Dinmohamed 2014). Prevalence data for MDS in the EU are available from few sources. Prevalence of MDS was estimated based on data from 22 European cancer registries through the RARECARE (Surveillance of Rare Cancers in Europe) project. The estimated complete prevalence as of 01 January 2008 was 24,958 persons in the EU, corresponding to a prevalence of 0.50 per 10,000 persons (Visser 2012). A prevalence of 0.50 per 10,000 population for MDS was also consistently reported from a systematic review of the literature on rare diseases in Europe (Orphanet, 2015). Recent data (2005-2014) from the HMRN in the United Kingdom estimate the 3-, 5-, and 10-year prevalence of MDS as 7.7, 9.9, and 12.2 per 100,000 persons, respectively (HMRN 2017). In addition, population-based data on MDS from the Dusseldorf MDS Registry in Germany during 1996 to 2005 indicated that the crude point prevalence of MDS according to the World Health Organisation classification was 1.14 per 10,000 persons (age-standardised prevalence: 0.72 per 10,000 in 2003, while the point prevalence of MDS according to the French-American-British classification was 1.28 per 10,000 persons (age-standardised prevalence: 0.81 per 10,000 persons) (Neukirchen 2011).

Demographics and the Target Population

Age

Myelodysplastic syndrome is a disease of the elderly, with a median age at diagnosis of over 70 years and with less than 10% of patients being younger than 50 years of age (Fenaux 2014; Neukirchen 2011). Similarly, the United Kingdom data demonstrated that the median age at diagnosis is 75.7 years (HMRN 2015).

Race

A review noted that although there are no known ethnic differences in the incidence of MDS, the disease tends to occur at an earlier age in Asian populations (Fenaux 2014). However, another review from the United States noted that MDS was most prevalent in Whites (Ma 2012)

Geography

Data from the HAEMCARE project (Sant 2010) that included data from 48 European cancer registries observed that for MDS, 66% of cases were in Ireland and the United Kingdom and 16% in Northern Europe; Central, Southern and Eastern Europe reported 7%, 9%, and 2%, respectively (Maynadié 2013).

Risk Factors for the Disease

A review noted that the aetiology of MDS is known in only 15% of cases (Fenaux 2014). An inherited predisposition to MDS should be assessed in patients with Down's syndrome, Fanconi anaemia, and neurofibromatosis, as well as MDS occurring in young adults or in families with other cases of MDS, acute myeloid leukaemia, or aplastic anaemia. Environmental factors could include previous use of chemotherapy, especially alkylating agents and purine analogues radiotherapy or ionizing radiation, and tobacco smoking. Recognized occupational factors include benzene and its derivatives, while excess MDS cases have also been observed in agricultural and industrial workers.

Main Treatment Options

The assessment of individual risk enables the identification of fit MDS patients with a poor prognosis who are candidates for upfront intensive treatments, primary allogenic stem cell transplantation. A high proportion of MDS patients are not eligible for potentially curative treatment due to advance age and/or clinically relevant comorbidities and poor performance status. In these patients, the therapeutic intervention is aimed at preventing cytopenia-related morbidity and preserving quality of life. In high-risk MDS patients, treatment using hypomethylating agents such as azacitidine is recommended. When azacitidine or decitabine administration is not possible, low-dose cytarabine is a treatment option for higher-risk MDS patients. For lower-risk MDS patients, the main priority is treatment of cytopenias, mainly anaemia. Chronic RBC transfusions, ESAs (ie, recombinant endogenous erythropoietin or darbepoetin, lenalidomide) are treatment options for low-risk MDS. Second-line treatments for low-risk MDS include anti-thymocyte globulin, hypomethylating agents, and lenalidomide. Iron chelation therapy is also used for low-risk MDS with favorable prognosis (Fenaux 2014).

Mortality and Morbidity

Patients with MDS have poor survival, with the 5-year relative survival being only 28.2% (HMRN, 2015). Specifically, according to the revised International Prognostic Scoring System (IPSS) for MDS, the median overall survival for patients in the different risk groups is as follows: 8.8 years for very low risk, 5.3 years for low risk, 3 years for intermediate risk, 1.6 years for high risk, and 0.8 years for very high-risk patients (Fenaux 2014).

SI.2. Concomitant Medication(s) in the Target Population

Chronic Renal Failure – Adult Patients

Comorbidity	Medications
Cardiovascular disease	Statins, fibrates, ACE inhibitors or beta blockers, angiotensin-II receptor antagonists, diuretics, anticoagulants, and antiplatelet medications
Hypertension	Classes of blood pressure medications include diuretics, beta blockers, ACE inhibitors, angiotensin-II receptor blockers, calcium channel blockers, alpha blockers, alpha-2 receptor agonist, and combined alpha and beta blockers
Diabetes mellitus	Insulin and oral hypoglycaemic agents
Hepatitis	Antiviral medications
Cancer	Chemotherapy, radiotherapy, hormonal therapy, drugs used for targeted therapy, and immunotherapy
Thrombosis	Anticoagulants, thrombolytic agents, antiplatelet medications

ACE=angiotensin-converting enzyme

Chronic Renal Failure – Paediatric Patients

Comorbidity	Medications
Hypertension	Classes of blood pressure medications include diuretics, beta blockers, ACE inhibitors, angiotensin-II receptor blockers, calcium channel blockers, alpha blockers, alpha-2 receptor agonist, and combined alpha and beta blockers
Hepatitis	Antiviral medications
Short stature	Growth hormone treatment
Thrombosis	Anticoagulants, thrombolytic agents, antiplatelet medications

ACE=angiotensin-converting enzyme

Cancer

Comorbidity	Medications
Hypertension	Classes of blood pressure medications include diuretics, beta blockers, ACE inhibitors, angiotensin-II receptor blockers, calcium channel blockers, alpha blockers, alpha-2 receptor agonist, and combined alpha and beta blockers
Diabetes	Insulin and other hypoglycaemic agents
Cardiovascular disease	Statins, fibrates, ACE inhibitors or beta blockers, angiotensin-II receptor antagonists, diuretics, anticoagulants, and antiplatelet medications
Renal failure	High blood pressure medications, medications to lower cholesterol levels, medications to relieve anaemia, anti-inflammatory medications, and medications to protect bones
Cerebrovascular disease	Aspirin, heparin, clopidogrel, warfarin, dipyridamole, tissue plasminogen activator
Myelosuppression/infection	Antibacterials for febrile neutropenia, colony-stimulating factors for neutropenia, possible blood transfusion for anaemia, or prophylactic administration of platelet concentrate

ACE=angiotensin-converting enzyme

Autologous Blood Donation

Autologous blood donation is a procedure and not a condition; therefore, there are no associated comorbidities.

Surgery

Comorbidity	Medications
Obesity	Prescription weight loss medication in certain situations
Osteoarthritis	Acetaminophen, nonsteroidal anti-inflammatory drugs, narcotics. Non-conservative treatments include cortisone injections and lubrication injections
Cardiovascular disease	Statins, fibrates, ACE inhibitors or beta blockers, angiotensin-II receptor antagonists, diuretics, anticoagulants, and antiplatelet medications
Hypertension	Classes of blood pressure medications include diuretics, beta blockers, ACE inhibitors, angiotensin-II receptor blockers, calcium channel blockers, alpha blockers, alpha-2 receptor agonist, and combined alpha and beta blockers

ACE=angiotensin-converting enzyme

Myelodysplastic Syndrome

Comorbidity	Medications
Cardiovascular disease	Statins, fibrates, ACE inhibitors or beta blockers, angiotensin-II receptor antagonists, diuretics, anticoagulants, and antiplatelet medications
Diabetes	Insulin and oral hypoglycaemic agents
Cerebrovascular diseases	Antihypertensives, cholesterol-lowering medications, antiplatelet medications, thrombolytics, anticoagulants, tissue plasminogen activator
Prior malignancies	Chemotherapy, radiotherapy, hormonal therapy, drugs used for targeted therapy, and immunotherapy

ACE=angiotensin-converting enzyme

SI.3. Important Comorbidities Found in the Target Population

Chronic Renal Failure – Adult Patients

Comorbidity: Cardiovascular Disease

Incidence of CVD:

Cardiovascular disease is frequently associated with CKD. In a population-based study in Germany, the IR of MI among persons with CKD was 146.5 per 10,000 PY in men and 48.2 per 10,000 PY in women (Meisinger 2006). A retrospective cohort study that used the US Medicare database observed a 13% increased rate of incident atrial fibrillation in patients with Stages 3 to 5 CRF (HR=1.13; 95% CI: 1.09-1.18) compared with patients without CRF (Nelson 2012).

Prevalence of CVD:

In a large, nationally representative sample of adults in England, heart failure was prevalent in 52.5%, ischaemic heart disease in 33.4%, and peripheral vascular disease in 36.3% of patients with CKD (Kearns 2013). In another UK study involving primary care computerised records, the prevalence of ischaemic heart disease was 25% for patients with CKD Stages 3 to 5 (de Lusignan 2005). Another UK study using the General Practice Research Database observed that 37.1% of patients with Stage 3 to 5 CKD also had CVD as did 27.7% of patients with Stage 5 CKD (Jameson 2014).

Mortality of CVD:

In a population-based German study, the CVD mortality rate among patients with CKD was 189.8 per 10,000 PY in men and 87.1 per 10,000 PY in women (Meisinger 2006). A review of the literature (Johnson 2007) concluded that CVD accounted for 40% to 50% of deaths in patients undergoing dialysis, and these populations have a 10- to 20-fold increased risk of cardiovascular mortality relative to age and sex-matched comparators without CKD. Similarly, in a retrospective cohort study that used US Medicare data, the 1-year mortality rate for Stages 3 to 5 CRF with incident atrial fibrillation was 35.6% (Nelson 2012).

Comorbidity: Hypertension

Incidence of hypertension:

Hypertension is very common among patients on haemodialysis or peritoneal dialysis, and those who have undergone renal transplant (Tedla 2011). Arterial hypertension develops in up to 80% of renal transplant recipients (Basić-Jukić 2007). The term “hypertension” in the discussion of incidence and prevalence is used as the inclusive term, and so may include occurrences of hypertensive crisis or other related terms.

Prevalence of hypertension:

In a large nationally representative sample of adults in England, hypertension was prevalent in 41.5% of patients with mildly impaired eGFR, 63.9% of those in Stage 3 to 5 CKD, and 79.3% of those in Stage 5 CKD (Jameson 2014). Hypertension prevalence was reported in 3.0% of all CKD patients in a US national survey of non-institutionalised adults (Saran 2015a), which

estimates that hypertension occurs in 35.8% of Stage 1, 48.1% of Stage 2, 59.9% of Stage 3, and 84.1% of Stage 4 to 5 patients with CRF (USRDS 2010). Similarly, in a Canadian population-based survey, the prevalence of hypertension in adults with CRF was 24.4% compared with 15% in patients without CRF. Furthermore, hypertension prevalence was more than double among those with Stage 3 to 5 CKD than with Stage 1 or 2 CKD (52.8% versus 23%, respectively) (Arora 2013). Among complications associated with hypertension in patients with CKD, heart failure may be exacerbated by anaemia (Silverberg 2006; Iaina 2005).

Mortality of hypertension:

In a meta-analysis of studies that included 25 general populations, 7 high-risk and 13 CKD cohorts, CKD emerged to be an equally relevant risk factor for mortality and ESRD in individuals without hypertension as in those with hypertension (Mahmoodi 2012b). Consistent with these findings, in a more recent large study of US veterans with CKD, all-cause mortality was increased both for patients in the lower (systolic blood pressure [SBP] <120 mm Hg and diastolic blood pressure [DBP] <80 mm Hg) and higher (SBP ≥160 mm Hg or DBP ≥100 mm Hg) blood pressure categories (Kovesdy 2013).

Comorbidity: Diabetes Mellitus

Incidence of diabetes mellitus:

In a Taiwanese national study of incident dialysis patients, the cumulative IR of new-onset diabetes was 4% at 1 year and 21% at 9 years (Tien 2013). In an older study based on a dialysis registry in Italy, the incidence of new diabetic patients admitted for dialysis per million population per year was 10.3 in women and 12.9 in men (Piccoli 1992).

Prevalence of diabetes mellitus:

Diabetes mellitus is a common comorbidity and cause of CRF and ESRD. In a large nationally representative sample of adults in England, diabetes mellitus was prevalent in 13.2% of patients with mildly impaired eGFR, and 19.2% of those with Stage 3 to 5 CKD (Jameson 2014). In the US adult population from 2007 to 2012, 39.2% of all CKD patients also had diabetes (Saran 2015a). Estimates were lower in a Canadian population-based survey, where the prevalence of diabetes mellitus in adults with CKD was 10.9% compared with 5.4% in patients without CKD. However, diabetes prevalence was more than double among those with Stage 3 to 5 CKD than with Stage 1 or 2 disease (23.4% versus 10.8%, respectively) (Arora 2013).

Mortality of diabetes mellitus:

According to US data linking NHANES and the national death index, standardised mortality among individuals with both diabetes and kidney disease was 31.1% (95% CI: 24.7%-37.5%) compared with 7.7% (95% CI: 7%-8.3%) among those without the 2 diseases (Afkarian 2013). In a Taiwanese study of incident dialysis patients, new-onset diabetes was associated with a 10% (95% CI: 3%-17%) increased mortality risk (Tien 2013).

Comorbidity: Hepatitis

Incidence of hepatitis:

The incidence of hepatitis C infection among 320 predialysis patients with CKD in Italy was estimated to be 6.25%, while the incidence in the general population in Europe ranged from 0.2% to 3.5% (Cavoli 2011). In a French study of 4,718 patients undergoing chronic haemodialysis, the estimated incidence of new hepatitis C infections per year was 0.05% (Saune 2011). In a US study of veterans with eGFR >60 mL/min•1.73 m^2 at baseline, patients who were hepatitis C virus (HCV) positive had an IR of 16.7 (16.4-17.0)/1,000 PY for developing an eGFR <60 mL/min•1.73 m^2 compared with 14.9 (14.8-15.0)/1,000 PY in the HCV-negative group. The adjusted HR for HCV was 1.15 (95% CI 1.12-1.17) (Molnar 2015).

Prevalence of hepatitis:

A recent update on hepatitis C prevalence in dialysis patients reported that the prevalence of hepatitis C among dialysis patients varies worldwide, ranging from a low of 1% to a high of over 70%. Notably, the prevalence of anti-hepatitis C positive patients on long-term dialysis in northern Europe is below 5% and around 10% in most of southern Europe (Fabrizi 2013). In a French study of 4,718 patients undergoing chronic haemodialysis, the prevalence of anti-hepatitis C antibodies (Abs) was 7.7% (Saune 2011).

Mortality of hepatitis:

A novel meta-analysis including 14 observational studies (n=145,608 unique patients on long-term dialysis) demonstrated that anti-HCV-positive serological status was an independent and significant risk factor for death in patients on maintenance dialysis (Fabrizi 2012). The summary estimate for adjusted RR (all-cause mortality) was 1.35 with a 95% CI of 1.25 to 1.47. The negative impact of HCV on all-cause survival in the dialysis population is consistent with other sources. The Dialysis Outcomes and Practice Patterns Study, a prospective observational study of representative samples of haemodialysis patients in France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States (16,720 patients followed up to 5 years) reported an independent and significant association between anti-HCV-positive serologic status and mortality (RR, 1.17; p<0.0159) (Goodkin 2003).

Comorbidity: Cancer

Incidence of cancer:

According to a review on CKD and cancer, kidney transplant recipients have a 3- to 4-fold increase in overall cancer risk compared with the general population, and RRs higher than 3 for about 20 specific tumours. After dialysis, cancer risk increases 10% to 80% according to studies for about 10 cancer sites (Stengel 2010).

Among 24,552 participants of a large population-based study in Sweden (Christensson 2013) that included older men (aged 60), younger men (aged 40 to 52), older women (aged 47 to 57), and younger women (aged 35 to 43), only 3.5% of patients had moderately impaired renal dysfunction at baseline. The proportion was higher in older patients (10% of men, 2% of women) than younger patients (7% of men, 1% of women). For participants with

GFR ≥60 mL/min/1.73 m^2 versus GFR <60 mL/min/1.73 m^2 at baseline, the 15-year probability of cancer was 23% versus 19% (older men), 7% versus 6% (younger men), 14% versus 13% (older women), and 10% versus 10% (younger women). No association was observed between moderately impaired renal function and overall long-term cancer risk except for an increased risk of kidney cancer (HR=3.38; 95% CI: 1.48-7.71) and moderately decreased GFR in younger men.

Similarly, in a population-based case-control study conducted among the US elderly by linking the Medicare and National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) programme data, ESRD was not associated with overall cancer risk, although risk was increased for specific tumours (Shebl 2012). Another US study of ESRD patients 18 years or older who received haemodialysis with no cancer diagnosis for the first 9 months of dialysis observed that the 5-year crude cumulative incidence of any cancer accounting for death as competing risk was 9.48% (95% CI 9.39%-9.57%) and a standardised incidence ratio of 1.42 (95% CI 1.41-1.43). This same study also observed that the cumulative incidence was higher for the following groups: person 65 years or older at dialysis therapy initiation (11.28%), men (10.93%), non-Whites (9.79%), non-Hispanics (9.65%), primary ESRD cause other than diabetes (hypertension, 10.39%). The risk was highest for cancers of the kidney/renal pelvis (standardised incidence ratio 4.03; 95% CI 3.88-4.19). In addition, having a HCV-positive status was associated with a greater risk of developing ESRD with an adjusted HR of 1.98 (95% CI 1.81-2.16). (Butler 2015)

In a large Australian prospective population-based cohort study (Wong 2009) of 3,654 residents aged 49 to 97 years, 711 (19.5%) cancers occurred during a mean follow-up period of 10 years. The cumulative incidence of cancer in men with CKD was 23.1 per 1,000 PY compared with 16.8 per 1,000 PY among those without CKD. After a mean follow-up period of 10 years, 23.3% of those with an eGFR <60 mL/min/1.73 m^2 had incident cancers compared with 16.9% of those with an eGFR >60 mL/min/1.73 m^2. In contrast, among women, cumulative incidence of cancers for those with CKD was 11.9 per 1,000 PY compared with 13.8 per 1,000 PY among those without CKD. A total of 12% of those with an eGFR <60 mL/min/1.73 m^2 developed cancers compared with 14% of those with an eGFR >60 mL/min/1.73 m^2.

Prevalence of cancer:

Among 79 patients with autosomal-dominant polycystic kidney disease (ADPKD) and CRF in a French hospital, 50 patients had ESRD and were on haemodialysis for more than 1 year or had received a transplant. Of 89 kidneys, 11 kidneys had carcinomas (Hajj 2009). A US study that used US Renal Data System ESRD incident data from 1998 to 2002 reported cancer prevalence of 31% in 236,009 ESRD patients at initiation of RRT (Xue 2005).

Mortality of cancer:

In a French prospective study of 155 elderly patients (≥80 years of age) with an eGFR below 45 mL/min/1.73 m^2, after a mean duration of 24.7 months follow up, 9% of deaths were due to cancer (Faller 2013). In another retrospective multicentre French study, of the 178 dialysis patients who developed cancer from 1997 to 2010 after initiation of chronic dialysis, 58% died during the 2-year follow-up period after cancer diagnosis (Janus 2013).

In a very recent prospective population-based cohort study from Australia, among 4,077 participants aged 49 to 97 years, the cumulative incidence of cancer deaths for those with an eGFR <60 mL/min/1.73 m^2 was 107 events/1,000 PY, compared with 95 events/1,000 PY for those with eGFR ≥60 mL/min/1.73 m^2 (Iff 2014).

Comorbidity: Thrombosis

Incidence of thrombosis:

Thrombosis, especially thrombosis of the arteriovenous fistula used for vascular access, is common in patients with ESRD. In a large longitudinal population-based study of middle-aged and elderly adults in the United States, the IR per 1,000 PY of venous thromboembolism (VTE) was 1.5 in patients with normal kidney function, 1.9 in those with mildly decreased renal function, and 4.5 in those with Stage 3 or 4 CRF (Wattanakit 2008). In a Netherlands study of 298 patients with nephrotic syndrome, the annual incidences of VTE and arterial thromboembolism were 1.02% and 1.48% respectively. Over the first 6 months of follow up, these rates were 9.85% and 5.52%, respectively (Mahmoodi 2008). Consistent findings were observed in another Netherlands study of 455 patients on dialysis in whom the IR of venous thrombosis was 5.6 times higher (95% CI: 3.1-8.9) than the rate in the general population (Ocak 2011).

Prevalence of thrombosis:

In a US study of 268 patients, those with CRF suffered more upper extremity deep vein thrombosis (DVT) than those without CRF (30% versus 10.8%, respectively) (Daneschvar 2008).

Mortality of thrombosis:

In a Netherlands study of 455 dialysis patients, the all-cause mortality risk was 1.9-fold (95% CI: 1.1-3.3) increased for patients with a history of venous thrombosis (Ocak 2011).

Chronic Renal Failure – Paediatric Patients

Comorbidity: Hypertension

Incidence of hypertension:

In a US prospective study of 140 children from 67 families with ADPKD, the incidence of hypertension in children with ADPKD was 18% (Fick 1994).

Prevalence of hypertension:

Hypertension is found in more than 50% of paediatric patients with CKD, although its prevalence varies according to the cause of CKD (Van DeVoorde 2011). For instance, in the Chronic Kidney Disease in Children cohort study, 37% of children with CKD had either elevated SBP or DBP (Flynn 2008), while the prevalence of hypertension was 79% in another US cross-sectional study of all (n=624) paediatric long-term haemodialysis patients (Chavers 2009).

Mortality of hypertension:

Mortality data associated with hypertension in the CKD paediatric population are not available.

Comorbidity: Hepatitis

Incidence of hepatitis:

Incidence data on hepatitis in children with CKD are not available.

Prevalence of hepatitis:

Hepatitis, especially hepatitis C, has been common among paediatric patients with ESRD receiving dialysis, sometimes affecting as many as 50% of patients on dialysis and 10% of those with CRF not requiring dialysis (Inglot 2000). Among 100 children with CRF (34 children on regular haemodialysis and 66 children on predialysis) in Egypt, 51% had exposure to hepatitis G virus, 5% tested positive for hepatitis B surface antigen, 5% tested positive for hepatitis B core antibody (Ab), and 52% had positive hepatitis C Ab (Hammad 2009).

Mortality of hepatitis in children:

The mortality rates associated with hepatitis infection in children with CKD are not available.

Comorbidity: Short Stature

Incidence of short stature:

Short stature is defined as a height below the 2 standard deviation score (SDS) for age and sex, which approximately corresponds to the 2.5 percentile; however, this statistical definition ideally should be used with an ethnically appropriate growth chart (Salas 2013; Oostdijk 2009). A study based on the European study group for nutritional treatment of CRF in childhood included 321 prepubertal patients treated for CRF due to congenital renal disorders. In this study, children with CRF had normal heights at birth but dropped below the third normal percentile during the first 15 months of life. The difference in growth rates resulted in a mean height SDS of -1.65±1.5 SDS and -2.79±1.4 SDS in groups with better and worse GFR, respectively (Schaefer 1996).

Prevalence of short stature:

Linear growth is frequently decreased in children with advanced CKD, but tends to improve with administration of recombinant human growth hormone (Kari 2005; de Graaff 2003; Mahesh 2008). The 2006 NAPRTCS Annual Report noted that children enroled in the registry had mean height deficits of -1.61 and -1.78 at dialysis initiation and transplantation, respectively (Seikaly 2006).

Mortality of short stature:

In a study of children receiving dialysis, each 1.0 SDS decrease in height was associated with a 14% increase in the risk of mortality (Wong 2000). Similarly, among patients receiving dialysis or with kidney transplants, those with moderate or severe growth failure had an increased risk of

hospitalisation and death (Furth 2002a). Finally, a height below the first percentile at dialysis initiation was associated with an increased risk of hospitalisation and death (Furth 2002b).

Cancer

Comorbidity: Hypertension

Incidence of hypertension:

Several studies report on the incidence of hypertension associated with various drug therapies in patients with cancer, with limited data on the overall incidence of hypertension in the general cancer population. For example, a retrospective cohort study was conducted to estimate the IRs of new-onset hypertension in adult cancer patients identified from the Varian Medical Oncology outpatient database in the United States. New-onset hypertension was observed in about one-third of 25,090 patients with various cancer types. The IRs of severe and crisis-level hypertension, respectively, were the highest in patients with gastric (18.5 cases per 100 PY and 5.6 per 100 PY, respectively) and ovarian cancer (20.2 per 100 PY and 4.8 per 100 PY, respectively). The highest IR of moderate hypertension was observed in patients with renal cancer (46.7 per 100 PY). Across all cancers, chemotherapy exposure was associated with a 2- to 3.5-fold increase in risk of any degree of hypertension compared with periods of no chemotherapy; higher hypertension levels demonstrated greater variability in RRs by type and line of therapy but indicated an overall increase associated with chemotherapy exposure (Fraeman 2013).

Prevalence of hypertension:

Among cancer patients, hypertension has been observed to be the most common comorbidity with a prevalence of 37% (Piccirillo 2004). However, a prevalence of 29% prior to chemotherapy has been found to be similar to the general population (Maitland 2010).

Mortality of hypertension:

Findings from a meta-analysis (Grossman 2002) of 10 longitudinal studies that evaluated the association between hypertension and cancer mortality in 47,119 patients observed that individuals with hypertension experienced an increased rate of cancer mortality during durations of follow up ranging from 9 to 20 years, with and age- and smoking-adjusted pooled odds ratio (OR) of 1.23 (95% CI 1.11 to 1.36). In 13 case-controlled studies, including 6,964 cases of renal cell cancer and 9.181 controls, the adjusted OR for renal cell cancer among hypertensive patients, relative to normotensive counterparts was 1.75 (95% CI 1.61 to 1.90). Based on 7 cohorts from Norway, Austria, and Sweden, a positive association was observed for cancer mortality for every 10-mmHg increment in men (HR=1.12; 95% CI: 1.08-1.15) and women (HR=1.06; 95% CI: 1.02-1.11), indicating a higher risk of death associated with elevated blood pressure (Stocks 2012).

Comorbidity: Diabetes

Incidence of diabetes:

The risk of new-onset diabetes among postmenopausal breast cancer survivors in a Canadian-based study began to increase 2 years after diagnosis (HR=1.07; 95% CI: 1.02-1.12) and rose even higher after 10 years (HR=1.21; 95% CI: 1.09-1.35) compared with women without breast cancer. The risk was highest in the first 2 years after diagnosis among those who received adjuvant chemotherapy (Lipscombe 2012). Another Canadian study assessed diabetes incidence in colorectal cancer (n=39,707) patients. The overall diabetes incidence was 8.7% over a mean follow-up time of 4.8 years. The overall diabetes incidence was higher in patients with no metastasis (10.6% versus 8.6%, $p<0.01$), and lower in patients who received chemotherapy (8.0% versus 9.0%) (Singh 2014).

Prevalence of diabetes:

In a US cancer registry study, excluding skin and haematologic malignancies, 15,951 cancer cases were identified, in whom the overall diabetes prevalence was 6.8%. Diabetes was common among patients with pancreatic (9.8%), colorectal (7.7%), or bladder (7.6%) cancers (Karlin 2012). Diabetes prevalence in patients with cancer admitted to a cancer hospital in the United Kingdom was reported to be 11%, and over half of the patients had gastrointestinal tract primary cancers (Morganstein 2012). However, diabetes prevalence (32.4%) was much higher in patients with cancer admitted to a Spanish hospital, with a greater prevalence observed in patients with prostate cancer (Sánchez Peralta 2012). A study of 40 patients with primary pancreatic cancer in Turkey reported recent-onset diabetes and impaired glucose tolerance in 32.5% and 5% of pancreatic patients, respectively (Cetin 2002).

Mortality of diabetes:

A meta-analysis of 15 studies that reported on postoperative cancer mortality associated with diabetes reported that pre-existing diabetes conferred a 50% increased risk of mortality in newly diagnosed patients with cancer after surgery (Barone 2010). Another meta-analysis reported that patients with breast cancer and diabetes had a significantly higher all-cause mortality risk (pooled HR 1.49; 95% CI: 1.35-1.65) compared with their nondiabetic counterparts (Peairs 2011). In a prospective study of participants recruited from German primary care practices, the incidence of deaths from cancer in patients with Type 2 diabetes (2.6%) was higher than in those without diabetes (1.2%) (Baur 2011). When investigated by cancer type in a US registry study, patients with pancreatic cancer who had coexisting diabetes had better overall survival than those without diabetes (HR=0.60; 95% CI: 0.44-0.80); however, the opposite was true for diabetic patients with prostate cancer (HR=1.36; 95% CI: 1.05-1.76) (Karlin 2012).

Comorbidity: Cardiovascular Disease

Incidence of CVD:

A nationwide study in Sweden observed a 70% greater overall incidence of coronary heart disease in patients with cancer compared with the general population without cancer. The IR was

highest for leukaemia and cancers of the small intestine, kidney, lung, and liver during the first 6 months of diagnosis (Zöller 2012).

In a large prospective study of patients with breast cancer in Denmark and Sweden, the incidence ratio of any heart disease among women who did not receive any radiation therapy for left- versus right-side breast cancer was 1.04 (95% CI: 1.00-1.09). Among women who received radiation therapy, the incidence ratio for left- versus right-side breast cancer was 1.08 (95% CI: 1.02-1.15) (McGale 2011). In a retrospective study of 271 patients with incident epithelial ovarian cancer in the United States, 49% experienced comorbid CVD during the study period (Shinn 2013). Reviews have also reported on the incidence of different types of cardiovascular morbidity (such as CHF) in relation to specific antineoplastic drugs (Senkus 2011; Khakoo 2008).

Prevalence of CVD:

Prevalence of comorbid CVD has been reported separately for specific cancer types in different studies. For instance, according to a US Medicare study of patients with breast cancer aged 66 years and older, the prevalence of CVD at the time of cancer diagnosis was 12.8% (Patnaik 2011). In a hospital-based study in Italy, of the 189 patients who underwent surgery for non-small cell lung cancer, 17.5% had concurrent CVD (Pavia 2007). However, a high prevalence of cardiovascular comorbidity of 52% has been observed among patients with metastatic colorectal cancer (Overbeek 2012). Finally, in 5,077 patients with prostate cancer in a US study, 256 had CHF or MI at baseline (Nanda 2009).

Mortality of CVD:

A US Medicare study of patients with breast cancer aged 66 years and older found CVD to be prevalent in 16.7% of deaths from breast cancer and 59.2% of deaths from other causes (Patnaik 2011). In a hospital-based study in Italy, of the 189 patients who underwent surgery for non-small cell lung cancer, 61% with concurrent CVD were alive at 5-year follow up (Pavia 2007). In a retrospective study of 271 patients with incident epithelial ovarian cancer in the United States, fewer than 15% of patients died within 1 month of developing a cardiovascular event (Shinn 2013).

Comorbidity: Renal Failure

Incidence of renal failure:

The incidence of contrast-induced nephropathy after contrast-enhanced computed tomography in hospitalised patients with cancer was 20% in a Turkish study (Cicin 2014). A nested case-control analysis involving patients newly diagnosed with prostate cancer using data extracted from the UK Clinical Practice Research Datalink reported 232 incident cases of acute kidney injury for an incident rate of 5.5 per 1,000 PY (Lapi 2013).

Prevalence of renal failure:

In the Belgian Renal Insufficiency and Anticancer Medications study, among 1,218 patients with cancer, the prevalence of elevated serum creatinine (≥1.2 mg/100 mL) was 14.9%, but 64% had

a GFR <90 mL/min/1.73 m^2 (Janus 2010). Similarly, the Renal Insufficiency and Anticancer Medications study, a French national observational study of nearly 5,000 patients, observed that 57.4% and 52.9% of patients had abnormal renal function or renal insufficiency when assessed using Cockcroft-Gault and Modification of Diet in Renal Disease formulae, respectively (Launay-Vacher 2007). Specifically, among 445 patients with lung cancer in the same study, 62.1% and 55.9% had abnormal renal function using the 2 formulae (Launay-Vacher 2009a); prevalence of abnormal renal function was 51.8% and 50.8% in 1,898 patients with breast cancer (Beuzeboc 2012) and 62.6% and 55.9% in 222 patients with prostate cancer (Launay-Vacher 2009b).

Mortality of renal failure:

In a Belgian retrospective study, among critically ill patients who received RRT for acute renal failure, those with haematologic malignancies (n=50 of 222) had higher crude intensive care unit (79.6% versus 55.7%) and in-hospital (83.7% versus 66.1%) mortality rates, and a higher mortality at 6 months (86% versus 72%) compared with those without haematologic malignancies. However, after adjustment for severity of illness and duration of hospitalisation before intensive care unit admission, haematologic malignancy by itself was no longer associated with higher risk of death (Benoit 2005).

Comorbidity: Cerebrovascular Disease

Incidence of cerebrovascular disease:

In a Swedish study, the observed number of strokes was 1,766 in 25,171 women with breast cancer, resulting in 12% increased risk (RR=1.12; 95% CI: 1.07-1.17). Most cerebrovascular events occurred in women aged 70 years and older at the time of breast cancer diagnosis. In women aged 55 to 69 years and 70 years and older, the risk of stroke was statistically significantly increased by 11% and 14% respectively, while there was no statistically significant increased risk of stroke in women younger than 55 years of age at the time of their breast cancer diagnosis (Nilsson 2005).

A US SEER-Medicare cohort of 6,862 patients with nonmetastatic head and neck cancer observed a 10-year incidence of cerebrovascular events in 34% in patients treated with radiotherapy alone, 25% in patients treated with surgery plus radiotherapy, and 26% in patients treated with surgery alone (Smith 2008). In another study of patients from a US cancer centre, of 195 stroke patients who had stroke diagnosed during 1997 to 2001, 96 patients had confirmed stroke during the study period, representing 0.12% of all admissions to the cancer centre. Stroke incidence by specific cancer type was as follows: 30% lung, 9% intracranial, 9% prostate, 4% breast, 6% lymphoma, 6% leukaemia, 6% gynaecologic, 6% bladder, 6% gastroesophageal, and 20% nonspecified (Cestari 2004).

Prevalence of cerebrovascular disease:

In a Swedish registry-based study, 868 women had a stroke before being diagnosed with breast cancer during 1970 to 2000 (Nilsson 2005). In a US SEER-Medicare study, the prevalence of

cerebrovascular disease was 8% in patients with ovarian cancer compared with 9.8% in women who were cancer free (Chia 2013).

Mortality of cerebrovascular disease:

A Swedish registry-based study of 25,171 women with breast cancer observed that stroke contributed to 7% of 12,840 deaths observed during follow up (Nilsson 2005). In a study of patients from a US cancer centre, the median overall survival was 4.5 months for 96 patients with a stroke diagnosis; 25% died within 30 days of their stroke (Cestari 2004).

Comorbidity: Myelosuppression/Infection

Incidence of myelosuppression:

In a US retrospective cohort chart review of patients with cancer, the incidence of Grade 3 or 4 myelosuppression was 22% in obese patients and 27% in non-obese patients. Of the patients who developed myelosuppression, 33% in the obese group and 20% in the non-obese group experienced myelosuppression on the first cycle of chemotherapy while the majority of myelosuppression occurred later in the chemotherapy cycles. In patients with lung cancer, the incidence of Grade 3 or 4 myelosuppression was higher than for rest of the cancer types in the study (Lopes-Serrao 2011).

Prevalence of myelosuppression:

Findings from a large US study including 387,319 hospitalised elderly patients with non-haematologic malignancies indicated that among those whose length of stay at the hospital was more than 10 days, 28.8% had neutropenia and 47.4% had infection (Shayne 2013).

Mortality of myelosuppression:

The same study above reported that, among patients who died, 16.2% had neutropenia and 20.2% had infection (Shayne 2013). Results from 2 systematic reviews on the impact of chemotherapy-induced myelosuppression on survival demonstrated that among 7 Phase 1 studies in patients with solid tumours, chemotherapy-related myelosuppression was associated with reduced mortality (HR=0.69; 95% CI: 0.61-0.77) (Lyman 2013).

Autologous Blood Donation

Autologous blood donation is a procedure and not a condition; therefore, there are no associated comorbidities.

Surgery

Comorbidity: Obesity in Elective Orthopaedic Surgery

Incidence of obesity in elective orthopaedic surgery:

There are no data published on the incidence of obesity in elective orthopaedic surgery.

Prevalence of obesity in elective orthopaedic surgery:

In a UK study of 385 patients who underwent TKR surgery, the overall prevalence of pre-operative obesity was 45%, while 15% of knee replacements were in highly obese (BMI ≥35) patients (Collins 2012). Another study using data from the Clinical Practice Research Datalink reported a mean BMI (kg/m^2) for female THR patients of 29.6 and for male THR patients of 28.8 (Culliford 2015). In a Norwegian study, increased BMI was strongly associated with an increased risk of TKR, with an adjusted HR of 6.16 (4.23-8.95) for those with a BMI >27.3 kg/m^2 (Apold 2014). Among US Medicare patients who underwent primary total knee arthroplasty between 1998 and 2010, 11.4% were obese. The rate of revision surgery within 12 months after primary total knee arthroplasty was significantly increased in obese patients (adjusted HR=1.19; 95% CI: 1.01-1.39) than in non-obese patients (Bozic 2014). In another US study conducted using a health maintenance organisation database, obesity was more prevalent in total knee arthroplasty patients (52%) than total hip arthroplasty patients (36%) (Namba 2005).

Mortality of obesity in elective orthopaedic surgery:

Mortality after elective orthopaedic surgery in general is not very high. In a prospective matched study of obese and non-obese patients in the United Kingdom who underwent TKR, no deaths were observed during the immediate perioperative period or within 3 months of the knee replacement. However, 1 death each in the obese and non-obese group was observed 3 years after revision for deep infection (obese patient) and 4 years after the primary surgery for the non-obese patient (Amin 2006). A US study using Nationwide Inpatient Sample (NIS) data comparing morbidly obese patients to matched controls reported an in-hospital mortality rate of 0.08% for morbidly obese patients after TKR compared with 0.02% for non-obese patients (OR: 32; 95% CI: 2.0.-5.2) (D'Apuzzo 2015).

Comorbidity: Osteoarthritis

Incidence of OA:

The incidence of OA is difficult to estimate due to its gradual progressive development and the problems of definition of new cases. However, it is estimated that for both men and women, the incidence of OA rises steeply after the age of 50, peaking in the 70- to 79-year-old age group (Eumusc.net 2014).

A prospective population-based cohort study in Sweden followed 11,026 men and 16,934 women for 11 years. In that study period, 471 individuals had knee OA and 551 individuals had hip OA (Lohmander 2009).

Prevalence of OA:

Prevalence of OA varies based on the age group of the population studied. Data collected as part of the Global Burden of Disease project (GBD 2010) estimate the standardised prevalence rate of hip OA per 100 population to be 4.20 in Denmark; 5.12 in Finland; 0.94 in Greece; 20.29 in Hungary; 1.61 in the 18- to 91-years old age group to 7.70 in the 65- to 99-years old age group in Italy; 6.80 in the 25- to 99-year-old age group to 51.29 in in the 60- to 89-years old age group in

Netherlands; 24.72 to 51.29 in people over 60 years in Spain; 3.88 in Sweden; and 26.28 in those >60 years old in the United Kingdom.

The standardised prevalence rate of knee OA per 100 population was reported as follows: 3.74 in Estonia; 6.55 in Greece; 28.30 in Hungary; 29.80 to 43.01 in the elderly in Italy; 6.95 to 43.01, depending on the age group studied, in the Netherlands; 35.12 to 71.10 in people >60 years old in Italy; 53.87 in Sweden; and 6.50 to 9.84 in the United Kingdom.

In a province-based study in Spain that included 7,577 participants, the derived prevalence of hip OA and knee OA were approximately 7.4% and 12.2%, respectively. The estimated appropriateness rate for hip replacement was 37.7% in men and 52.7% in women with OA, with the same for knee replacement (11.8% in men and 17.9% in women with OA (Quintana 2008).

Mortality of OA:

In a population-based cohort study in the southwest of England, among 1,163 patients with OA, 438 deaths were observed. Patients with OA had 55% excess all-cause mortality compared with the general population (standardised mortality ratio: 1.55; 95% CI: 1.41-1.70). Excess mortality was also observed for all disease-specific causes of death but was especially pronounced for cardiovascular- and dementia-associated mortality (Nüesch 2011).

However, of 1,998 primary THR and TKRs performed for OA in patients aged ≥75 years in a single institution in Finland, mortality was 0.15% at 30 days, 0.35% at 90 days, 1.60% at 1 year, 7.6% at 3 years, and 16% at 5 years; this was similar following hip and knee replacement, indicating low postoperative mortality in healthy elderly joint replacement recipients (Jämsen 2013a). Similarly, a Danish nationwide epidemiologic study to assess mortality for patients undergoing THR for OA reported 20% lower overall short-term (0-90 days) mortality (mortality rate ratio: 0.8; 95% CI: 0.7 to 0.9) and 30% lower long-term mortality (up to 12.7 years) in comparison with general population controls (Pedersen 2011).

Comorbidity: Cardiovascular Disease

Incidence of CVD:

A retrospective nationwide cohort study within the Danish national registries that included 95,227 patients who underwent a primary THR or TKR surgery between January 1998 and December 2007 observed an absolute 6-week risk of acute MI to be 0.51% in THR patients and 0.21% in TKR patients. The risk of acute MI was substantially increased in the first 2 weeks after THR (25-fold) and TKR (31-fold) surgery compared with controls (Lalmohamed 2012). Another Danish study using data covering THRs and TKRs over a 6-year period observed that 0.7% experienced a major adverse cardiovascular event within 30 days after elective TKR or THR (Thornqvist 2014). A US analysis of hospital discharges from 2008 to 2011 reported the incidence of in-hospital acute MI was 0.20% after THR or TKR (Menendez 2015). Similarly, results from a hospital-based study in the United Kingdom that analysed postoperative outcomes in 2,090 patients admitted with an acute hip fracture over a 4-year period observed that heart failure (5%) was a common postoperative complication (Roche 2005).

In a Canadian study of 1,744 adults with validated OA, 173 (9.9%) participants had a primary total joint arthroplasty. Of these, 153 participants were successful matched based on propensity scores with a participant who did not have the procedure. Overall, 111 (36.3%) cardiovascular events occurred in the matched cohort of 153 pairs, and participants who underwent a total joint arthroplasty were 44% less likely to have experienced a cardiovascular event (HR=0.56; 95% CI: 0.43-0.74) during follow up (Ravi 2013).

Prevalence of CVD:

In the Danish nationwide cohort study above, the prevalence of ischaemic heart disease and CHF in THR patients was 12.5% and 7.9%, respectively, and in TKR patients was 11.8% and 5%, respectively (Lalmohamed 2012). Similarly, in a Finnish registry-based study of THR and TKR performed for primary OA, the following prevalence of CVDs was reported: 12% coronary heart disease, 5.4% atrial fibrillation, and 3.5% heart failure for THR recipients, and 12.5% coronary heart disease, 5.8% atrial fibrillation, and 4.4% heart failure for TKR recipients (Jämsen 2013b). Another study that included patients in the United Kingdom reported 24.8% of TKR patients in the United Kingdom also had heart disease (Oleske 2014).

Mortality of CVD:

The Thornqvist study cited above also reported a 30-day mortality rate from cardiovascular causes of 0.2% and a 1-year mortality rate from cardiovascular causes of 0.8% after TKR or THR surgery (Thornqvist 2014).

Findings from a hospital-based study in the United Kingdom that analysed postoperative outcomes in 2,090 patients admitted with an acute hip fracture over a 4-year period observed mortality rates of 9.6% at 30 days and 33% at 1 year. In patients who developed postoperative heart failure (5%), mortality was 65% at 30 days, and of these patients, 92% were dead within 1 year (Roche 2005). In another UK study of 467 patients who underwent hip fracture surgery at a hospital, acute coronary syndrome was the cause of death in 31.4% of the 35 patients who died (Khan 2013).

Comorbidity: Hypertension

Incidence of hypertension:

There are no data published on the incidence of hypertension in elective orthopaedic surgery.

Prevalence of hypertension:

Data from a Finnish registry-based study that included 43,747 THR recipients and 53,007 TKR recipients performed for OA reported hypertension prevalence to be 17.7% in THR recipients and 20.8% in TKR recipients (Jämsen 2013b). Another study that included patients in the United Kingdom reported 49.3% of TKR patients also had hypertension (Oleske 2014).

In a large US study of 3,960 same-day, 172-Staged 0-3, and 1,533-Staged 3-12 bilateral total knee arthroplasties (TKAs), the prevalence of hypertension in the 3 groups were 50.8%, 57%, and 66.8%, respectively, while the rates for pulmonary hypertension was 1.6%, 2.9%, and 2.6%,

respectively (Poultsides 2014). Another US study compared the way in which the National Hospital Discharge Survey (NHDS) and the NIS reported data on THR. In this study, the NHDS reported that 54% of THR patients had hypertension as a comorbid condition and the NIS reported 58% (Bekkers 2014).

Mortality of hypertension:

In the study by Poultsides et al above (Poultsides 2014), hypertension was not associated with major morbidity and mortality in patients who underwent same-day bilateral TKAs, but patients with pulmonary hypertension had over 2 times the risk (OR=2.34; 95% CI: 1.08-5.08) compared with those who did not have the comorbidity. Another similar US study that used the largest inpatient database to identify total knee athroplasty and total hip arthroplasty entries observed that patients with pulmonary hypertension undergoing total hip arthroplasty experienced an approximately 4-fold increased adjusted risk of mortality (2.4% versus 0.6%), and those undergoing total knee athroplasty had a 4.5-fold increased adjusted risk of mortality (0.9% versus 0.2%) compared with patients who did not have pulmonary hypertension (Memtsoudis 2010).

Myelodysplastic Syndrome

Comorbidity: Cardiovascular Disease

Incidence of CVD:

Cardiovascular disease is often the most frequently reported comorbidity in MDS patients. In a US study of 512 MDS patients, of the 303 (59.2%) patients who had no history of cardiac disease, 188 (62%) patients developed cardiac disease during a 3-year follow up, compared with 54.5% of the Medicare population. Age-adjusted analyses revealed that MDS was associated with a more than 2-fold increased risk of cardiac-related events (Goldberg 2010).

Prevalence of CVD:

In an Austrian MDS cohort of 616 patients, the prevalence of cardiac disease was 25.2% (n=155) and CVD was 28.4% (n=175). Specifically, at baseline, 18.3% had coronary heart disease, cardiac insufficiency, or MI, 9.3% had arrhythmia, and 3.4% had valvular heart disease (Bammer 2014). Another cohort of 840 MDS patients in an Italian trial observed that cardiac disease was the most frequently observed (25%) comorbidity. The frequency of individual cardiac events was as follows: arrhythmia, 7%; heart valve disease, 2%; coronary artery disease of MI, 8%; and CHF or ejection fraction <50%, 19%. This study also included a validation cohort of 504 MDS patients from Germany, in who the prevalence of cardiac diseases was higher at 39% (Della Porta 2011). This was also observed in another Italian study of 418 patients with a prevalence of cardiac disease of 28.4%; specifically, 10% had infarction, 21% had coronary heart disease without infarction, 50% had cardiomyopathy, 19% had cardiac valve disease, ad 50% had arrhythmia (Breccia 2011). A US study of 512 elderly MDS patients observed a prevalence of 19.3% for cardiac events, 48.2% for MIs, 51.2% for CHF, and 51.2% for arrhythmias. Overall, 73.2% of MDS patients experienced any cardiac events, which was significantly higher that 54.5% of the Medicare population (Goldberg 2010).

Mortality of CVD:

Data from a cohort of 840 MDS patients in an Italian trial observed that 63% of non-leukemic deaths in these patients was due to cardiac failure, and cardiac disease was independently related to the risk of non-leukemic death (HR: 3.57) in a multivariate analysis (Della Porta 2011). Similarly, in a US study of 1,708 elderly MDS patients, those with CHF (20.8%) had a 35% increased risk of mortality (HR: 1.35, 95% CI: 1.16-1.57) than patients without the condition (Wang 2009).

Comorbidity: Diabetes

Incidence of diabetes:

Diabetes has also been frequently observed in MDS patients in the literature. In a US study of 512 MDS patients, of the 380 patients who had no history of diabetes, 82 (21.6%) developed diabetes during a 3-year follow up (Goldberg 2010).

Prevalence of diabetes:

In an Austrian MDS cohort of 616 patients, the prevalence of diabetes was 12.2% (n=75) (Bammer 2014). Another cohort of 840 MDS patients in an Italian study observed that 11% had diabetes (Della Porta 2011), while an Italian study of 418 patients observed diabetes in 18.7% of patients, with organ damage in 20 patients (Breccia, 2011). In a study of 171 patients from the Dusseldorf MDS Registry in Germany, diabetes was the most frequent comorbidity observed in 21 patients (Zipperer 2009). A US study of 1,708 MDS patients observed that 21.8% had diabetes and 5.9% had diabetes with sequelae (Wang 2009). Another US study of 512 MDS patients observed diabetes prevalence of 40% in these patients, higher compared with 33.1% in the Medicare population (Goldberg 2010).

Mortality of diabetes:

Data from a cohort of 840 MDS patients in an Italian study observed that diabetes was not independently related to the risk of non-leukaemic death in a multivariate analysis (Della Porta 2011). Similarly, in a US study of 1,708 elderly MDS patients, diabetes did not appear to affect survival (Wang 2009).

Comorbidity: Hypertension

Incidence of hypertension:

Incidence data on hypertension in MDS patients is not available as data on hypertension are mostly available as case reports and small series.

Prevalence of hypertension:

In a US study of 600 MDS patients, approximately 55% of patients were diagnosed with a disorder of the cardiovascular system, with hypertension being the most common comorbidity at 37% (Naqvi 2011). A small retrospective chart review of 26 patients who had received a diagnosis of both chronic myeloid disorders and pulmonary hypertension observed 2 patients had

MDS (Dingli 2001). Another study of 88 patients observed hypertension to be present in 45.4% of patients (De Roos 2010).

Mortality of hypertension:

Not described.

Comorbidity: Cerebrovascular Disease

Incidence of cerebrovascular disease:

Not described.

Prevalence of cerebrovascular diseases:

In an Austrian MDS cohort of 616 patients, the prevalence of cerebrovascular disease was 7.1% (n=44) (Bammer 2014). Another cohort of 840 MDS patients in an Italian study observed that 5% of patients had cerebrovascular disease (Della Porta 2011). A US study of 1,708 MDS patients observed that 8% had cerebrovascular disease (Wang 2009).

Mortality of cerebrovascular diseases:

Data from a cohort of 840 MDS patients in an Italian study observed that cerebrovascular disease was not independently related to risk of non-leukaemic death in a multivariate analysis (Della Porta 2011). Similarly, in a US study of 1,708 elderly MDS patients, cerebrovascular disease, which was present in 8% of patients, did not appear to affect survival (Wang 2009).

Cormorbidity: Prior Malignancies

Incidence of prior malignancies:

No incidence estimates can be computed, as by definition, prior malignancies will have occurred before MDS diagnosis.

Prevalence of prior malignancies:

In an Austrian MDS cohort of 616 patients, the prevalence of prior tumour was 9.9% (n=61) (Bammer 2014). Another cohort of 840 MDS patients in an Italian study observed that 10% had solid tumours at any time point in the patient's history, excluding non-melanoma skin cancer (Della Porta 2011), while an Italian study of 418 patients observed tumours in 6% of patients (Breccia 2011). Yet another study of 11 patients from the Dusseldorf MDS Registry in Germany observed 9 patients with a solid tumour (Zipperer 2009).

Mortality of prior malignancies:

Data from a cohort of 840 MDS patients in an Italian study observed that solid tumour was independently related to risk of non-leukaemic death (HR: 2.61) in a multivariable analysis (Della Porta 2011). However, in a US study of 1,708 elderly MDS patients, the most frequently reported cause of death was neoplasm, accounting for 888 (56.6%) deaths, and among patients who died from neoplasm, 42.5% were reported to have died from MDS and 38.4% died from leukaemia (Wang 2009).

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

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

Active substance	Epoetin alfa
Product(s) concerned	EPREX ERYPO ERYPO FS
MAH/MAA name	Janssen-Cilag Pharma GmbH, Austria JANSSEN-CILAG GmbH, Germany Janssen-Cilag NV, Belgium Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag International NV, Cyprus Janssen-Cilag s.r.o., Czech Republic Janssen-Cilag A/S, Denmark Janssen-Cilag OY, Finland JANSSEN-CILAG, France Janssen-Cilag Pharmaceutical S.A.C.I., Greece Janssen-Cilag Limited Janssen-Cilag SpA, Italy Janssen-Cilag, NV, Luxembourg Janssen-Cilag International NV, Malta Janssen-Cilag BV, Netherlands Janssen-Cilag AS, Norway Janssen-Cilag Farmaceutica, Lda, Portugal Janssen-Cilag S.A. Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag S.A., Spain Janssen-Cilag AB, Sweden Janssen-Cilag Ltd, United Kingdom

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Key Safety Findings From Nonclinical Studies

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
Toxicity findings include:	
Single & repeat-dose toxicity	
No acute toxicities were observed at single epoetin alfa doses up to 20,000 units/kg in mice and rats (oral, IM, and IV) or in dogs (IV). Findings observed after single-dose administration of epoetin alfa included moderate increases in erythropoiesis in bone marrow, mucoid faeces, and slight elevations of lactate dehydrogenase in dogs at 20,000 units/kg, as well as changes in haematology parameters due to the pharmacological activity of epoetin alfa (eg, such as increases in HCT, HGB, and reticulocyte counts), which were observed in both the single-dose and in all repeated-dose toxicity studies. Repeated-dose studies of up to 13 weeks were conducted in monkeys (SC, IV), while studies of up to 52-weeks duration were conducted in rats (IP) and dogs (SC, IV). The major toxicology findings observed following repeated epoetin alfa administration to animals were related to polycythaemia that developed as a result of prolonged overstimulation of RBC production. Overstimulation of RBC production resulted in premature deaths in rats and dogs in the chronic studies, with mortality rates approaching 80% in rats at 250 units/kg/day and 50% in dogs at doses ≥100 units/kg/day. As a result of high systemic epoetin alfa concentrations, extramedullary haematopoiesis was seen in spleen and liver, and depletion of iron stores and myelofibrosis was seen in the bone marrow in rats and dogs. The increased severity with time and/or dose suggests a potential for bone marrow toxicity resulting from sustained or marked stimulation of erythropoiesis.	In repeated-dose toxicologic studies in dogs and rats, but not in monkeys, epoetin alfa therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of CRF in humans and may be related to secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis was not increased in a study of patients on haemodialysis who were treated with epoetin alfa for 3 years compared with a matched control group of dialysis patients who had not been treated with epoetin alfa (SmPC Section 5.3). An increased incidence of TVEs has been observed in patients receiving ESAs (SmPC Sections 4.4 and 4.8). These include venous and arterial thromboses and embolism (including some with fatal outcomes), such as DVT, pulmonary emboli, retinal thrombosis, and MI. Additionally, cerebrovascular accidents (including cerebral infarction, cerebral haemorrhage, and transient ischaemic attacks) have been reported.

Key Safety Findings From Nonclinical Studies

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
Changes in platelet count seen in rats and dogs suggest a role for erythropoietin in the terminal stage of megakaryocyte maturation leading to platelet release. A shift toward the production of proerythroblasts at the expense of megakaryocytes may occur with continued dosing, the timing of the shift being dependent on dosage. These data suggest that, although changes in platelet counts may occur, the risk of these changes resulting in thrombosis appeared small.	
Kidney and lung thrombi were observed at the higher epoetin alfa dose levels in rats dosed for 52 weeks, but thrombi were not observed in the dog or monkey studies.	
Toxicology studies were not conducted in renally impaired animals.	
Reproductive toxicity	
The administration of epoetin alfa does not impair fertility in rats.	There is no relevance to humans.
Developmental toxicity	
The administration of epoetin alfa does not result in embryo-foetal toxicity in rats or rabbits. A peri-and postnatal developmental toxicology study in rats showed no effect on maturation of offspring.	Findings in the toxicology studies were interpreted as being secondary to decreased maternal body weight gain when given in weekly doses of approximately 20 times the recommended human dose; therefore, the significance to humans is unknown when given at therapeutic dose levels. Findings in animal studies do not represent a developmental toxicity of the drug, but rather, are due to polycythaemia seen in the dams.
In animal studies, epoetin alfa has been shown to decrease foetal body weight, delay ossification, and increase foetal mortality when given in weekly doses of approximately 20 times the recommended human weekly dose.	
Findings from repeated-dose toxicology studies in juvenile dogs and monkeys were consistent with those seen in adult animals.	

Key Safety Findings From Nonclinical Studies

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
Hepatotoxicity	
Systemic toxicity studies did not show hepatotoxicity and therefore no further hepatoxicity studies were conducted.	There are no nonclinical data to indicate that there would be any hepatotoxicity in humans.
Genotoxicity	
Epoetin alfa does not induce bacterial gene mutation (Ames test), chromosomal aberrations in mammalian cells, gene mutation at the hypoxanthine-guanine phosphoriosyltransferase locus, nor micronuclei in mice administered IV doses up to 500,000 units/kg.	These studies demonstrate that epoetin alfa has low potential to inflict genetic damage when administered to humans.
Carcinogenicity	
As EPREX is a biotechnology-derived pharmaceutical product, rodent carcinogenicity studies were not conducted, consistent with ICH S6(R1) guidance. Long-term carcinogenicity studies have not been conducted. 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. Nonclinical studies have shown that treatment with ESAs does not enhance tumour progression directly or through enhanced angiogenesis/vasculogenesis.	The risk of tumour initiation or proliferation of established tumours is unclear from preclinical data. Disease progression has been determined to be an important potential risk for the product. A clinical trial is ongoing (EPO-ANE-3010) to assess disease progression in anaemic patients with metastatic breast cancer receiving EPREX and chemotherapy. Refer to SVII.3 for additional details regarding Trial EPO-ANE-3010.
General safety pharmacology findings:	
Cardiovascular (including potential for QT interval prolongation)	

Key Safety Findings From Nonclinical Studies

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
In cardiovascular assessments in guinea pigs and dogs, vehicle and epoetin alfa at a concentration of 1,000 units/mL suppressed contractile force or contraction rate in the isolated guinea pig atria. In conscious dogs, there were transient increases in heart rate at 20 and 2,000 units/kg epoetin alfa IV (transient and slightly decreased at 200 unit/kg) and slight decreases in mean blood pressure at 200 and 2,000 units/kg epoetin alfa IV. Slightly increased R-wave heights and R-R intervals were observed in all dose groups.	Nonclinical in vitro studies were conducted up to 1,000 IU/mL, which is approximately 1,000 times the achieved maximum plasma exposure of epoetin alfa when administered at 40,000 IU/mL once per week. Therefore, there is no anticipated risk of QT prolongation to patients.
Nervous system	
Epoetin alfa administered to mice and rats via IP doses of 450 and 1,500 units/kg TIW for 3 weeks did not affect brain excitability in mice, did not alter water content or electrolyte distribution of the cerebral cortex, cerebellum, or subcortex in rats, and did not affect electrolyte contributions in rat plasma or cerebrospinal fluid. In mice, rats, and rabbits administered IV doses of 20, 200, or 2,000 units/kg, epoetin alfa did not have significant effects on general behaviour, motor coordination, analgesia, hexobarbital-induced sleeping time, anticonvulsion, and spontaneous electroencephalogram led from the amygdaloid, hippocampus, and the cortices of motor, sensory, and visual areas, and spinal reflex. A decrease in body temperature was seen in rats administered 2,000 units/kg IV epoetin alfa; no other evidence of depression or stimulation of the central nervous system was noted at the same dose.	There are no risks identified in nonclinical studies that haven't been adequately addressed in clinical trials.
Other - Immunogenicity	
Antibodies to erythropoietin can be generated in preclinical species. In repeated-dose toxicology studies, Ab titres were of low frequency, but the Ab response can be stimulated by the use of adjuvants and an aggressive immunisation schedule.	There are no risks identified in nonclinical studies that haven't been adequately addressed in clinical trials. The risk of PRCA was first identified in postauthorisation usage and is considered an important identified risk and is described in detail in Module SVII.3 of this RMP.

Key Safety Findings From Nonclinical Studies

Key Safety Findings (from nonclinical studies)	Relevance to Human Usage
Mechanisms for drug interactions	
None	Not applicable
Other toxicity-related information or data	
None	Not applicable

Ab=antibody; CRF=chronic renal failure; DVT=deep vein thrombosis; ESA=erythropoiesis-stimulating agent; HCT=haematocrit; HGB=haemoglobin; ICH=International Council for Harmonisation; IM=intramuscular; IP=intraperitoneal; IV=intravenous; MI=myocardial infarction; PRCA=pure red cell aplasia; RBC=red blood cell, RMP= risk management plan; SC=subcutaneous; TIW=3 times per week; TVE=thrombotic vascular event

SII. Conclusions on Nonclinical Data

No nonclinical safety signals have been detected that are relevant for the clinical setting because most derive from polycythaemia (exaggerated pharmacology of epoetin alfa) or an immune response due to epoetin alfa being foreign in animals.

Nonclinical Safety Concerns

Important identified risks	
None	Not applicable
Important potential risks	
None	Not applicable
Missing information	
None	Not applicable

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

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

Active substance	Epoetin alfa
Product(s) concerned	EPREX ERYPO ERYPO FS
MAH/MAA name	Janssen-Cilag Pharma GmbH, Austria JANSSEN-CILAG GmbH, Germany Janssen-Cilag NV, Belgium Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag International NV, Cyprus Janssen-Cilag s.r.o., Czech Republic Janssen-Cilag A/S, Denmark Janssen-Cilag OY, Finland JANSSEN-CILAG, France Janssen-Cilag Pharmaceutical S.A.C.I., Greece Janssen-Cilag Limited Janssen-Cilag SpA, Italy Janssen-Cilag, NV, Luxembourg Janssen-Cilag International NV, Malta Janssen-Cilag BV, Netherlands Janssen-Cilag AS, Norway Janssen-Cilag Farmaceutica, Lda, Portugal Janssen-Cilag S.A. Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag S.A., Spain Janssen-Cilag AB, Sweden Janssen-Cilag Ltd, United Kingdom

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SIII.1. Brief Overview of Development

EPREX solution for injection is Janssen-Cilag's proprietary medicinal product containing the active substance epoetin alfa, a purified glycoprotein hormone of recombinant DNA origin that stimulates erythropoiesis (recombinant human erythropoietin [r-HuEPO]). EPREX is formulated as a sterile, colourless solution for IV and SC administration. The initial dossier to the EU, submitted as Concertation Procedure No. 3 (Directive 87/22/EEC), received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) in June 1988 for the use of EPREX in the treatment of adult patients with CRF on haemodialysis (IV route of administration). EPREX solution for injection is marketed as prefilled syringes under several trade names including EPREX throughout most of the world, ERYPO in Germany and Austria, and PROCRIT® in the United States.

The use of EPREX is currently approved in 97 countries worldwide for the treatment of anaemia in patients with CRF (dialysis and predialysis) and supportive anaemia care and reduction of transfusion requirements in adults with cancer receiving chemotherapy (Annex 3). It has also been approved in several countries as a facilitator of ABD and in several countries to reduce allogeneic blood requirements in the perisurgical setting.

Since the original 1988 EU approval, the following extensions to the therapeutic use of EPREX have been granted in the EU:

- Adult patients with CRF with renal insufficiency not yet undergoing dialysis; IV and SC routes of administration (July 1990)
- Adult patients with CRF on haemodialysis; SC route of administration (December 1991)
- Adult patients with CRF on chronic ambulatory peritoneal dialysis; SC route of administration (December 1992)
- Paediatric patients with CRF on haemodialysis; IV route of administration (March 1993)
- Adult patients with cancer receiving platinum-containing chemotherapy; SC route of administration (May 1994)
- Patients donating autologous blood prior to surgery; IV route of administration (June 1994)
- Patients undergoing elective, orthopaedic surgery; SC route of administration (February 1998)

Chronic Renal Failure Indication

Data from 30 clinical trials with patient-level data (n=7,656 patients treated with EPREX) in the CRF indication are included in the analyses of exposure and risk in the following sections. More studies have been conducted over the years to support label changes and new dosage forms that form the basis of the efficacy and safety of EPREX in this patient population.

Cancer Indication

Data from 46 clinical trials with patient-level data (n=5,827 patients treated with EPREX) in the cancer indication are included in the analyses of exposure and risk in the following sections. As with the CRF indication, more studies have been conducted over the years to support label changes and new dosage forms that form the basis of the efficacy and safety of EPREX in this patient population.

In the following exposure tables, the cancer indication is designated oncology.

Autologous Blood Donation Indication

Seven clinical trials that enroled a total of 644 patients (242 treated with placebo and 402 with epoetin alfa) were conducted to form the basis for evaluation of efficacy and safety of epoetin alfa in increasing the yield of autologous blood in patients participating in an ABD programme before elective surgery.

Surgery Indication

The efficacy and safety of epoetin alfa in patients undergoing orthopaedic surgery was demonstrated in 11 clinical trials. A total of 2,940 patients undergoing orthopaedic surgery were evaluated. Most patients were treated for 10 days to 3 weeks before elective surgery.

Although epoetin alfa is approved for use in conjunction with elective orthopaedic surgery, Trial H87-083, which enroled 182 patients, was conducted in patients undergoing coronary artery bypass graft surgery (Annex 4).

Data from 8 trials with patient-level data are included in the analyses of exposure and risk in the following sections.

MDS Population

Two randomised, double-blind, placebo-controlled clinical trials were conducted to form the basis for the evaluation of efficacy and safety of epoetin alfa in the treatment of anaemic patients with MDS. Trial EPO-ANE-3018 was conducted to demonstrate that epoetin alfa treatment reduces the proportion of anaemic patients with IPSS low- or intermediate-1 risk MDS who require any transfusion, compared with placebo, through Week 48. Due to poor patient enrolment, the study was terminated early. Therefore, the total final enrolment was 25 patients, with 8 patients assigned to the epoetin alfa 40,000 IU group, 9 patients to the epoetin alfa 80,000 IU group, and 9 patients to the placebo group. Trial EPOANE3021 was conducted to demonstrate the effectiveness of epoetin alfa in inducing and maintaining erythroid response, significantly reducing the percentage of patients requiring transfusion, and prolonging the time to first RBC transfusion in patients with IPSS low- or intermediate-1 risk MDS. A total of 130 patients in Europe were randomised, with 85 patients assigned to the epoetin alfa group and 45 patients assigned to the placebo group.

SIII.2. Clinical Trial Exposure

The clinical trial database from which information is summarised in this document is limited to the clinical trials for which patient-level data are available. As the start of the clinical trial programme for EPREX dates back to the mid-1980s, available data are presented below. The following sections describe the overall clinical trial programme with a data cutoff date of 30 June 2015, with Tables 1 to 20 summarising available patient-level data. This database includes 93 trials that enroled over 21,000 patients, of whom >70% (15,339 patients) were exposed to epoetin alfa.

Exposure in Randomised Controlled Clinical Trials

Tabular summaries of completed randomised, controlled epoetin alfa clinical trials are provided in Annex 4 for the CRF, cancer, ABD, surgery, and MDS indications.

Exposure to EPREX in randomised, controlled clinical trials for which patient-level data are available, is summarised in Tables 1 through 10 by duration, dose, age and sex, race, and baseline hepatic and renal status (renal status only for the cancer, ABD, surgery, and MDS indications).

In the randomised, controlled trials population of 7,595 EPREX-treated patients:

- There were 33,583.7 person-months exposure to EPREX (Tables 1 and 2)
- A total of 2,361 (31%) were men and 5,234 (69%) patients were women (Tables 5 and 6)
- A total of 2,524 (33%) patients were 65 years of age or older, while 781 (10%) patients were 75 years of age or older (Tables 5 and 6)
- A majority of patients (5,169 [68%]) were White, while 353 (5%) patients were Black, and 528 patients (7%) were Asian, Hispanic or Latino, American Indian or Alaska Native, or Other (Tables 7 and 8); data on ethnic and racial origin were missing for 1,545 (20%) patients
- A total of 4,920 (65%) of the 7,538 patients in the cancer, ABD, surgery, or MDS trials captured in the laboratory database had mild (creatinine clearance [CRCL] >50 to <80 mL/min; n=1,910), moderate (CRCL ≥30 to <50 mL/min; n=565), or severe (CRCL ≤30 mL/min; n=60) renal impairment at baseline (Tables 9 and 10); CRCL data at baseline were missing or noted as normal in the database for 2,385 patients (Note: only trials associated with the cancer, ABD, surgery, and MDS indications were included in this evaluation because CRF was evaluated as a separate indication by itself.)

Table 1 : Exposure by Duration; All Randomised Controlled Clinical Trials

INDICATION: CHRONIC RENAL FAILURE - DIALYSIS		
Duration of Exposure	Persons (N=97)	Person-months
Cumulative up to 1 month	5	2.33
Cumulative up to 3 months	25	41.1
Cumulative up to 6 months	33	79.84
Cumulative up to 9 months	97	465.38
Cumulative up to 12 months	97	465.38
Cumulative up to 18 months	97	465.38
Cumulative up to 24 months	97	465.38

Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004

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INDICATION: CHRONIC RENAL FAILURE - PREDIALYSIS		
Duration of Exposure	Persons (N=464)	Person-months
Cumulative up to 1 month	57	31.54
Cumulative up to 3 months	227	339.61
Cumulative up to 6 months	335	867.38
Cumulative up to 9 months	343	926.85
Cumulative up to 12 months	358	1091.48
Cumulative up to 18 months	384	1461.55
Cumulative up to 24 months	443	2813.57
Cumulative up to 36 months	459	3203.81
Cumulative up to 48 months	463	3385.95
Missing	1	.

Chronic Renal Failure – Predialysis Trials: EPO-AUS-14, EPO-CAN-10, EPO-ITA-7, EPOCKD2002, G86-011, H87-054

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INDICATION: ONCOLOGY		
Duration of Exposure	Persons (N=5323)	Person-months
Cumulative up to 1 month	608	195.42
Cumulative up to 3 months	2221	3773.04
Cumulative up to 6 months	4205	12126.16
Cumulative up to 9 months	4533	14452.93
Cumulative up to 12 months	4757	16907.93
Cumulative up to 18 months	5082	21239.29
Cumulative up to 24 months	5189	23440.69
Cumulative up to 36 months	5270	25744.23
Cumulative up to 48 months	5306	27228.81
Cumulative up to 60 months	5312	27563.1
Cumulative up to 72 months	5317	27897.43
Cumulative up to 84 months	5318	27972.7
Missing	5	.

Oncology Trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20 and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-ANE-3010, EPO-CAN-29

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INDICATION: AUTOLOGOUS BLOOD DONATION		
Duration of Exposure	Persons (N=402)	Person-months
Cumulative up to 1 month	316	199.49
Cumulative up to 3 months	389	311.36
Cumulative up to 6 months	399	349.6
Cumulative up to 9 months	400	356.04
Cumulative up to 12 months	400	356.04
Cumulative up to 18 months	400	356.04
Cumulative up to 24 months	400	356.04
Missing	2	.

ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058

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INDICATION: SURGERY		
Duration of Exposure	Persons (N=1207)	Person-months
Cumulative up to 1 month	1106	638.32
Cumulative up to 3 months	1164	718.75
Cumulative up to 6 months	1166	726.05
Cumulative up to 9 months	1166	726.05
Cumulative up to 12 months	1166	726.05
Cumulative up to 18 months	1166	726.05
Cumulative up to 24 months	1166	726.05
Missing	41	.

Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, PR97-19-002 (spine)

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INDICATION: MDS		
Duration of Exposure	Persons (N=102)	Person-months
Cumulative up to 1 month	6	2.37
Cumulative up to 3 months	18	27.53
Cumulative up to 6 months	60	247.39
Cumulative up to 9 months	67	297.3
Cumulative up to 12 months	102	677.59
Cumulative up to 18 months	102	677.59
Cumulative up to 24 months	102	677.59

MDS Trials: EPO-ANE-3018 and EPOANE3021

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Table 2: Exposure by Duration (Totals); All Randomised Controlled Clinical Trials

	INDICATION: ALL	
Duration of Exposure	Persons (N=7595)	Person-months
Cumulative up to 1 month	2098	1069.47
Cumulative up to 3 months	4044	5211.4
Cumulative up to 6 months	6198	14396.42
Cumulative up to 9 months	6606	17224.54
Cumulative up to 12 months	6880	20224.46
Cumulative up to 18 months	7231	24925.9
Cumulative up to 24 months	7397	28479.31
Cumulative up to 36 months	7494	31173.09
Cumulative up to 48 months	7534	32839.82
Cumulative up to 60 months	7540	33174.11
Cumulative up to 72 months	7545	33508.44
Cumulative up to 84 months	7546	33583.7
Missing	49	.

Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004
Chronic Renal Failure – Predialysis Trials: EPO-AUS-14, EPO-CAN-10, EPO-ITA-7, EPOCKD2002, G86-011, H87-054.
Oncology Trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20 and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010
ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058
Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, PR97-19-002 (spine)
MDS Trials: EPO-ANE-3018 and EPOANE3021

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Table 3: Exposure by Dose; All Randomised Controlled Clinical Trials

INDICATION: CHRONIC RENAL FAILURE - DIALYSIS		
Initial dose level	Persons (N=97)	Person-months
10-50 IU/kg QW	6	10.71
51-200 IU/kg QW	13	21.19
51-100 IU/kg TIW	78	433.48
Total	97	465.38

QW=once weekly; TIW=3 times a week
Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004.

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INDICATION: CHRONIC RENAL FAILURE - PREDIALYSIS		
Initial dose level	Persons (N=464)	Person-months
1-50 IU/kg TIW	28	51.61
51-100 IU/kg TIW	72	117.22
101-300 IU/kg TIW	30	42.15
1,001-5,000 IU QW	211	2680.31
10,001-20,000 IU QW	1	13.47
10,000-20,000 IU Q2W	116	469.03
Missing	6	12.16
Total	464	3385.95

QW=once weekly; Q2W=once every 2 weeks; TIW=3 times a week
NOTE: One of the 464 patients is missing exposure data and is not included in the calculation of person-months.
Chronic Renal Failure – Predialysis Trials: EPO-AUS-14, EPO-CAN-10, EPO-ITA-7, EPOCKD2002, G86-011, H87-054.

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INDICATION: ONCOLOGY		
Initial dose level	Persons (N=5323)	Person-months
600 IU/kg QW	228	912.36
100 IU/kg TIW	65	98.76
150 IU/kg TIW	1367	4442.12
300 IU/kg TIW	124	490.18
40,000 IU QW	2437	18699.93
60,000-80,000 IU Q2W	7	26.74
120,000 IU Q3W	4	13.34
4,000-5,000 IU TIW	125	230.31
10,000 IU TIW	964	3057.18
Missing	2	1.77
Total	5323	27972.7

QW=once weekly, Q2W=once every 2 weeks; Q3W=once every 3 weeks; TIW=3 times a week
NOTE: Five of the 5,323 patients are missing exposure data and are not included in the calculation of person-months.
Oncology Trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20 and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-ANE-3010, EPO-CAN-29

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INDICATION: AUTOLOGOUS BLOOD DONATION		
Initial dose level	Persons (N=402)	Person-months
Dose level 150 IU/kg BIW	29	16.76
Dose level 300 IU/kg BIW	53	32.59
Dose level 600 IU/kg BIW	177	105.4
Dose level 300 IU/kg TIW	71	88.71
Dose level 600 IU/kg TIW	72	112.59
Total	402	356.04

BIW=2 times a week; TIW=3 times a week
NOTE: Two women (1 in the 18- to 39-year age group and 1 in the 50- to 59-year age group) are missing exposure data and are not included in the calculation of person-months.
ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058

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INDICATION: SURGERY		
Initial dose level	Persons (N=1207)	Person-months
100 IU/kg QD	172	82.33
150 IU/kg QD	63	16.46
300 IU/kg QD	365	239.44
600 IU/kg QW	341	228.14
40,000 IU QW	241	159.67
Missing	25	.
Total	1207	726.05

QD=once daily; QW=once weekly
NOTE: Forty-one of the 1,207 patients are missing exposure data and are not included in the calculation of person-months.
Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, PR97-19-002 (spine)

[TSUB03E.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub03e.sas] 09OCT2015, 14:55

INDICATION: MDS		
Initial dose level	Persons (N=102)	Person-months
450 IU/kg QW	85	603.7
40,000 IU QW	8	23.39
80,000 IU QW	9	50.5
Total	102	677.59

MDS=myelodysplastic syndrome; QW=once weekly
MDS Trials: EPO-ANE-3018 and EPOANE3021

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Table 4: Exposure by Dose (Totals); All Randomised Controlled Clinical Trials

	INDICATION: ALL	
Initial dose level	Persons (N=7595)	Person-months
100 IU/kg QD	172	82.33
150 IU/kg QD	63	16.46
300 IU/kg QD	365	239.44
1-50 IU/kg QW	6	10.71
51-200 IU/kg QW	13	21.19
450 IU/kg QW	85	603.7
600 IU/kg QW	569	1140.5
150 IU/kg BIW	29	16.76
300 IU/kg BIW	53	32.59
600 IU/kg BIW	177	105.4
1-50 IU/kg TIW	28	51.61
51-100 IU/kg TIW	215	649.46
101-300 IU/kg TIW	1592	5063.16
600 IU/kg TIW	72	112.59
1,001-5,000 IU QW	211	2680.31
10,001-30,000 IU QW	1	13.47
40,000 IU QW	2686	18882.99
80,000 IU QW	9	50.5
10,000-20,000 IU Q2W	116	469.03
60,000-80,000 IU Q2W	7	26.74
120,000 IU Q3W	4	13.34
500-5,000 IU TIW	125	230.31
5,001-15,000 IU TIW	964	3057.18
Missing	33	13.93
Total	7595	33583.7

BIW=2 times a week; QD=once daily; QW=once weekly; Q2W=every 2 weeks; Q3W=every 3 weeks; TIW=3 times a week;
NOTE: Forty-nine of the 7,595 patients are missing exposure data and are not included in the calculation of person-months.
Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004
Chronic Renal Failure – Predialysis Trials: EPO-AUS-14, EPO-CAN-10, EPO-ITA-7, EPOCKD2002, G86-011, H87-054.
Oncology Trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20 and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010
ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058
Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, PR97-19-002 (spine)
MDS Trials: EPO-ANE-3018 and EPOANE3021

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Table 5: Exposure by Age Group and Gender; All Randomised Controlled Clinical Trials

	INDICATION: CHRONIC RENAL FAILURE - DIALYSIS			
	Men		Women	
Age Group	Persons (N=57)	Person-months	Persons (N=40)	Person-months
<18 years	0	-	0	-
18 - 39 years	23	125.3	14	73.92
40 - 49 years	9	40.74	9	44.35
50 - 59 years	8	41.30	10	49.64
60 - 64 years	5	22.74	4	7.43
65 - 69 years	5	30.06	1	2.00
70 - 74 years	5	8.61	2	7.29
75 - 79 years	2	12.02	0	0.00
80 - 84 years	0	-	0	-
>=85 years	0	-	0	-
Missing	0	0.00	0	0.00

Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004

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	INDICATION: CHRONIC RENAL FAILURE - PREDIALYSIS			
	Men		Women	
Age Group	Persons (N=226)	Person-months	Persons (N=238)	Person-months
<18 years	0	0.00	1	4.57
18 - 39 years	23	251.6	29	277.7
40 - 49 years	31	276.2	29	387.1
50 - 59 years	42	310.7	29	150.6
60 - 64 years	28	173.7	23	304.7
65 - 69 years	35	176.5	25	153.9
70 - 74 years	31	243.4	15	105.0
75 - 79 years	17	109.7	18	89.89
80 - 84 years	6	27.60	21	96.36
>=85 years	13	55.82	48	191.1
Missing	0	0.00	0	0.00

NOTE: One of the 464 patients is missing exposure data and is not included in the calculation of person-months.
Chronic Renal Failure – Predialysis Trials: EPO-AUS-14, EPO-CAN-10, EPO-ITA-7, EPOCKD2002, G86-011, H87-054.

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	INDICATION: ONCOLOGY			
	Men		Women	
Age Group	Persons (N=1504)	Person-months	Persons (N=3819)	Person-months
<18 years	137	561.1	107	581.4
18 - 39 years	36	122.3	403	2681
40 - 49 years	135	390.8	852	5323
50 - 59 years	315	952.0	1170	7734
60 - 64 years	243	740.1	505	3196
65 - 69 years	271	818.1	342	1876
70 - 74 years	216	640.1	280	1265
75 - 79 years	104	281.8	119	562.5
80 - 84 years	35	99.02	30	103.7
>=85 years	12	19.22	11	23.85
Missing	0	0.00	0	0.00

NOTE: Five of the 5,323 patients are missing exposure data and are not included in the calculation of person-months.
Oncology Trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20 and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-ANE-3010, EPO-CAN-29

[TSUB05C.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub05c.sas] 09OCT2015, 14:55

	INDICATION:AUTOLOGOUS BLOOD DONATION			
	Men		Women	
Age Group	Persons (N=143)	Person-months	Persons (N=259)	Person-months
<18 years	3	1.77	3	1.84
18 - 39 years	24	27.66	28	29.21
40 - 49 years	20	21.88	21	19.02
50 - 59 years	35	39.29	63	62.29
60 - 64 years	27	23.23	43	36.47
65 - 69 years	15	11.33	42	29.27
70 - 74 years	14	8.97	33	24.54
75 - 79 years	3	1.77	17	10.71
80 - 84 years	2	1.22	8	4.90
>=85 years	0	0.00	1	0.66
Missing	0	0.00	0	0.00

NOTE: Two women (1 in the 18- to 39-year age group and 1 in the 50- to 59-year age group) are missing exposure data and are not included in the calculation of person-months.
ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058

[TSUB05D.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub05d.sas] 09OCT2015, 14:55

INDICATION: SURGERY

	Men		Women	
Age Group	Persons (N=368)	Person-months	Persons (N=839)	Person-months
<18 years	0	-	0	-
18 - 39 years	24	16.66	47	28.98
40 - 49 years	33	16.23	84	56.15
50 - 59 years	67	29.90	143	92.91
60 - 64 years	63	28.48	109	72.71
65 - 69 years	73	37.13	126	80.99
70 - 74 years	41	25.66	132	77.80
75 - 79 years	41	23.95	116	74.61
80 - 84 years	19	11.33	61	36.27
>=85 years	6	3.58	21	12.71
Missing	1	0.00	0	0.00

NOTE: Forty-on of the 1,207 patients are missing exposure data and are not included in the calculation of person-months.
Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, PR97-19-002 (spine)

[TSUB05E.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub05e.sas] 09OCT2015, 14:55

INDICATION: MDS

	Men		Women	
Age Group	Persons (N=63)	Person-months	Persons (N=39)	Person-months
<18 years	0	-	0	-
18 - 39 years	0	-	0	-
40 - 49 years	1	1.64	1	5.49
50 - 59 years	3	10.48	1	8.34
60 - 64 years	4	24.41	3	22.14
65 - 69 years	8	59.47	4	22.77
70 - 74 years	15	102.18	12	76.32
75 - 79 years	16	103.98	7	53.16
80 - 84 years	8	52.01	8	65.12
>=85 years	8	42.35	3	27.73
Missing	0	0.00	0	0.00

MDS Trials: EPO-ANE-3018 and EPOANE3021

[TSUB05G.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub05g.sas] 09OCT2015, 14:56

Table 6: Exposure by Age Group and Gender (Totals); All Randomised Controlled Clinical Trials

	INDICATION: ALL			
	Men		Women	
Age Group	Persons (N=2361)	Person-months	Persons (N=5234)	Person-months
<18 years	140	562.89	111	587.83
18 - 39 years	130	543.51	521	3091.06
40 - 49 years	229	747.53	996	5835.60
50 - 59 years	470	1383.75	1416	8097.77
60 - 64 years	370	1012.63	687	3639.56
65 - 69 years	407	1132.58	540	2165.29
70 - 74 years	322	1028.90	474	1556.24
75 - 79 years	183	533.22	277	790.83
80 - 84 years	70	191.18	128	306.33
>=85 years	39	120.97	84	256.03
Missing	1	0.00	0	0.00

NOTE: Forty-nine of the 7,595 patients are missing exposure data and are not included in the calculation of person-months.
Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004
Chronic Renal Failure – Predialysis Trials: EPO-AUS-14, EPO-CAN-10, EPO-ITA-7, EPOCKD2002, G86-011, H87-054.
Oncology Trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20 and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010
ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058
Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, PR97-19-002 (spine)
MDS Trials: EPO-ANE-3018 and EPOANE3021

[TSUB06.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub06.sas] 09OCT2015, 14:56

Table 7: Exposure by Ethnic and Racial Origin; All Randomised Controlled Clinical Trials

INDICATION: CHRONIC RENAL FAILURE - DIALYSIS

Race	Persons (N=97)	Person-months
White	86	412.48
Black or African American	1	6.08
Asian	3	12.29
American Indian or Alaska Native	1	6.01
Hispanic or Latino	0	0.00
Other [a]	6	28.52
Missing	0	0.00
Total	97	465.38

[a] Other races include MISSING (6).
Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004

[TSUB07A.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub07a.sas] 09OCT2015, 14:56

INDICATION: CHRONIC RENAL FAILURE - PREDIALYSIS

Race	Persons (N=464)	Person-months
White	382	2966.67
Black or African American	48	147.75
Asian	12	126.36
American Indian or Alaska Native	1	5.03
Hispanic or Latino	6	25.03
Other a	15	115.12
Missing	0	0.00
Total	464	3385.95

a Other races include ABORIGINAL (1), COOK ISLAND (2),EAST-INDIAN (2), MAORI(3), NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER (1), RUSSIAN (1), SAMOAN (1) and MISSING (4).
NOTE: One of the 464 patients is missing exposure data and is not included in the calculation of person-months.
Chronic Renal Failure – Predialysis Trials: EPO-AUS-14, EPO-CAN-10, EPO-ITA-7, EPOCKD2002, G86-011, H87-054.

[TSUB07B.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub07b.sas] 09OCT2015, 14:56

INDICATION: ONCOLOGY

Race	Persons (N=5323)	Person-months
White	3270	17908.40
Black or African American	143	421.29
Asian	366	4397.96
American Indian or Alaska Native	3	6.37
Hispanic or Latino	29	100.47
Other [a]	52	487.36
Missing	1460	4650.84
Total	5323	27972.70

[a] Other races include AFGHAN(1), ANTILLEAN(2), ARAB(1), ASIAN-FILIPINO(2), CARIBBEAN (1), COLOURED(2), EAST-INDIAN(3), EGYPTIAN(1), FIJIAN(1), FIRST NATIONS (NATIVE)(1), GUATEMALAN(1), GYPSY(2), HALF-CASTE(3), HISPANIC(12), INDIAN(1), MESTIZA(1), MIXED RACE(3), MIXED- ASIAN/AFRICAN(1), MOTHER-ASIAN/FATHER CAUCASIAN(1), NATIVE HAWAIIAN(1), PHILIPINO(1), PORTUGESE(1), SURINAM(1), TRINIDADIAN(1) and MISSING (7).
NOTE: Five of the 5,323 patients are missing exposure data and are not included in the calculation of person-months.
Oncology Trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20 and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO_INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-ANE-3010, EPO-CAN-29

[TSUB07C.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub07c.sas] 09OCT2015, 14:56

INDICATION: AUTOLOGOUS BLOOD DONATION		
Race	Persons (N=402)	Person-months
White	372	338.07
Black or African American	24	14.29
Asian	0	0.00
American Indian or Alaska Native	0	0.00
Hispanic or Latino	0	0.00
Other [a]	6	3.68
Missing	0	0.00
Total	402	356.04

[a] Other races include INDIAN (1) and MISSING (5).
NOTE: Two women (1 in the 18- to 39-year age group and 1 in the 50- to 59-year age group) are missing exposure data and are not included in the calculation of person-months.
ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058

[TSUB07D.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub07d.sas] 12OCT2015, 10:20

INDICATION:SURGERY		
Race	Persons (N=1207)	Person-months
White	1042	631.23
Black or African American	137	80.69
Asian	5	1.91
American Indian or Alaska Native	0	0.00
Hispanic or Latino	15	9.30
Other [a]	8	2.92
Missing	0	0.00
Total	1207	726.05

[a] Other races include CAPE VERDIAN (1) and MISSING (7).
NOTE: Forty-one of the 1,207 patients are missing exposure data and are not included in the calculation of person-months.
Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, PR97-19-002 (spine)

[TSUB07E.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub07e.sas] 09OCT2015, 14:56

INDICATION: MDS		
Race	Persons (N=102)	Person-months
White	17	73.89
Black or African American	0	0.00
Asian	0	0.00
American Indian or Alaska Native	0	0.00
Hispanic or Latino	0	0.00
Other	0	0.00
Missing	85	603.70
Total	102	677.59

MDS Trials: EPO-ANE-3018 and EPOANE3021

[TSUB07G.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub07g.sas] 09OCT2015, 14:56

Table 8: Exposure by Ethnic and Racial Origin and (Totals); All Randomised Controlled Clinical Trials

	INDICATION:ALL	
Race	Persons (N=7595)	Person-months
White	5169	22330.74
Black or African American	353	670.09
Asian	386	4538.51
American Indian or Alaska Native	5	17.41
Hispanic or Latino	50	134.80
Other	87	637.60
Missing	1545	5254.54
Total	7595	33583.70

NOTE: Forty-nine of the 7,595 patients are missing exposure data and are not included in the calculation of person-months.
Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004
Chronic Renal Failure – Predialysis Trials: EPO-AUS-14, EPO-CAN-10, EPO-ITA-7, EPOCKD2002, G86-011, H87-054.
Oncology Trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20, and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010
ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058
Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, PR97-19-002 (spine)
MDS Trials: EPO-ANE-3018 and EPOANE3021

[TSUB08.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub08.sas] 09OCT2015, 14:56

Table 9: Exposure by Special Population; All Randomised Controlled Clinical Trials

INDICATION: CHRONIC RENAL FAILURE - DIALYSIS

Population	Category at Baseline	Persons	Person-months
Total		(N=97)	
Hepatic Impairment		(n=97)	
ALT			
	<=ULN (normal)	76	361.76
	>ULN to <=2.5 x ULN	12	57.33
	>2.5 to <=5.0 x ULN	3	18.04
	>5.0 to <=20.0 x ULN	1	6.01
	>20.0 x ULN	0	0.0
	Missing	5	
AST			
	<=ULN (normal)	88	414.16
	>ULN to <=2.5 x ULN	6	33.12
	>2.5 to <=5.0 x ULN	2	12.09
	>5.0 to <=20.0 x ULN	0	0.0
	>20.0 x ULN	0	0.0
	Missing	1	
Bilirubin			
	<=ULN (normal)	96	459.37
	>ULN to <=1.5 x ULN	0	0.0
	>1.5 to <=3.0 x ULN	0	0.0
	>3.0 to <=10.0 x ULN	0	0.0
	>10.0 x ULN	0	0.0
	Missing	1	
Alkaline phosphatase			
	<=ULN (normal)	72	332.85
	>ULN to <=2.5 x ULN	21	108.85
	>2.5 to <=5.0 x ULN	3	17.61
	>5.0 to <=20.0 x ULN	1	6.08
	>20.0 x ULN	0	0.0
	Missing	0	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; N/n=number; ULN=upper limit of normal; x=times
Of the 97 patients in the Chronic Renal Failure – Adult Haemodialysis dataset, 97 patients had at least one non-missing hepatic ALT, AST, bilirubin, or alkaline phosphatase measurement. For each parameter measured, some of the 97 patients did not have data available and are counted as missing.
Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004

[TSUB09A.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub09a.sas] 09OCT2015, 14:56

INDICATION: CHRONIC RENAL FAILURE - PREDIALYSIS			
Population	Category at Baseline	Persons	Person-months
Total		(N=464)	
Hepatic Impairment		(n=395)	
ALT			
	<=ULN (normal)	365	2790.54
	>ULN to <=2.5 x ULN	10	105.76
	>2.5 to <=5.0 x ULN	0	0.0
	>5.0 to <=20.0 x ULN	0	0.0
	>20.0 x ULN	0	0.0
	Missing	20	
AST			
	<=ULN (normal)	345	2438.18
	>ULN to <=2.5 x ULN	7	81.54
	>2.5 to <=5.0 x ULN	0	0.0
	>5.0 to <=20.0 x ULN	0	0.0
	>20.0 x ULN	0	0.0
	Missing	43	
Bilirubin			
	<=ULN (normal)	363	3072.69
	>ULN to <=1.5 x ULN	0	0.0
	>1.5 to <=3.0 x ULN	1	0.03
	>3.0 to <=10.0 x ULN	0	0.0
	>10.0 x ULN	0	0.0
	Missing	31	
Alkaline phosphatase			
	<=ULN (normal)	309	2291.48
	>ULN to <=2.5 x ULN	72	699.79
	>2.5 to <=5.0 x ULN	2	19.61
	>5.0 to <=20.0 x ULN	0	0.0
	>20.0 x ULN	0	0.0
	Missing	12	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; N/n=number; ULN=upper limit of normal; x=times
Person-months may be underestimated due to missing exposure data.
Of 464 patients in the Chronic Renal Failure – Adult Predialysis dataset, 395 patients had at least one non-missing hepatic ALT, AST, bilirubin, or alkaline phosphatase measurement. For each parameter measured, some of the 395 patients did not have data available and are counted as missing.
Chronic Renal Failure – Predialysis Trials: EPO-AUS-14, EPO-CAN-10, EPO-ITA-7, EPOCKD2002, G86-011, H87-054.
[TSUB09B.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub09b.sas] 09OCT2015, 14:56

INDICATION: ONCOLOGY			
Population	Category at Baseline	Persons	Person-months
Total		(N=5323)	
Hepatic Impairment[a]		(n=3130)	
ALT			
	<=ULN (normal)	2442	15793.28
	>ULN to <=2.5 x ULN	482	3868.58
	>2.5 to <=5.0 x ULN	74	469.55
	>5.0 to <=20.0 x ULN	31	198.14
	>20.0 x ULN	10	46.29
	Missing	91	
AST			
	<=ULN (normal)	2334	14996.40
	>ULN to <=2.5 x ULN	636	4902.93
	>2.5 to <=5.0 x ULN	77	507.83
	>5.0 to <=20.0 x ULN	31	172.81
	>20.0 x ULN	8	32.23
	Missing	44	
Bilirubin			
	<=ULN (normal)	2719	18711.33
	>ULN to <=1.5 x ULN	109	825.79
	>1.5 to <=3.0 x ULN	39	188.78
	>3.0 to <=10.0 x ULN	180	723.68
	>10.0 x ULN	36	117.19
	Missing	47	
Alkaline phosphatase			
	<=ULN (normal)	1869	11983.08
	>ULN to <=2.5 x ULN	786	6260.99
	>2.5 to <=5.0 x ULN	183	1474.96
	>5.0 to <=20.0 x ULN	55	387.91
	>20.0 x ULN	9	39.16
	Missing	228	
Renal impairment		(n=3372)	
	Mild (CrCl>50 to <80 mL/min)	1342	8477.14
	Moderate (CrCl>30 to <=50 mL/min)	339	1791.84
	Severe (CrCl<=30 mL/min)	43	139.14
	Missing or Other[b]	1648	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CrCl=creatinine clearance; min=minute; N/n=number; x=times; ULN-upper limit of normal

Person-months may be underestimated due to missing exposure data.

[a] Of the 5,323 patients in the oncology dataset, 3,130 patients had data measuring hepatic impairment. For each parameter measured, some patients did not have data available and are counted as missing.

[b] Of the 3,372 patients with CrCl data, only 1,724 patients were categorized as mild, moderate, or severe with respect to renal impairment. The remaining 1,648 patients were normal or missing baseline CrCl.

Oncology Studies: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20, and OEOU21), NON-CISPLATIN (I88-037, OEO-U22, and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-ANE-3010, EPO-CAN-29

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INDICATION:AUTOLOGOUS BLOOD DONATION			
Population	Category at Baseline	Persons	Person-months
Total		(N=402)	
Hepatic Impairment[a]		(n=398)	
ALT			
	<=ULN (normal)	367	317.80
	>ULN to <=2.5 x ULN	27	24.05
	>2.5 to <=5.0 x ULN	2	2.56
	>5.0 to <=20.0 x ULN	0	0.0
	>20.0 x ULN	0	0.0
	Missing	2	
AST			
	<=ULN (normal)	378	330.41
	>ULN to <=2.5 x ULN	18	14.00
	>2.5 to <=5.0 x ULN	0	0.0
	>5.0 to <=20.0 x ULN	0	0.0
	>20.0 x ULN	0	0.0
	Missing	2	
Bilirubin			
	<=ULN (normal)	384	326.60
	>ULN to <=1.5 x ULN	9	14.23
	>1.5 to <=3.0 x ULN	0	0.0
	>3.0 to <=10.0 x ULN	0	0.0
	>10.0 x ULN	0	0.0
	Missing	5	
Alkaline phosphatase			
	<=ULN (normal)	367	322.10
	>ULN to <=2.5 x ULN	28	20.53
	>2.5 to <=5.0 x ULN	0	0.0
	>5.0 to <=20.0 x ULN	0	0.0
	>20.0 x ULN	0	0.0
	Missing	3	
Renal impairment		(n=390)	
	Mild (CrCl>50 to <80 mL/min)	141	118.74
	Moderate (CrCl>30 to <=50 mL/min)	40	30.42
	Severe (CrCl<=30 mL/min)	5	3.55
	Missing or Other[b]	204	

ABD=autologous blood donation; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CrCl=creatinine clearance; N/n=number; ULN=upper limit of normal; x=times
Person-months may be underestimated due to missing exposure data.
[a] Of the 402 patients in the ABD dataset, 398 patients had data measuring hepatic impairment. For each parameter measured, some patients did not have data available and are counted as missing.
[b] Of the 390 patients with CrCl data, only 186 patients were categorized as mild, moderate, or severe with respect to renal impairment. The remaining 204 patients were normal or missing baseline CrCl.
ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058

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INDICATION:SURGERY			
Population	Category at Baseline	Persons	Person-months
Total		(N=1207)	
Hepatic Impairment[a]		(n=830)	
ALT			
	<=ULN (normal)	533	250.09
	>ULN to <=2.5 x ULN	51	23.72
	>2.5 to <=5.0 x ULN	2	0.76
	>5.0 to <=20.0 x ULN	2	0.99
	>20.0 x ULN	0	0.0
	Missing	242	
AST			
	<=ULN (normal)	758	441.86
	>ULN to <=2.5 x ULN	68	41.07
	>2.5 to <=5.0 x ULN	2	0.53
	>5.0 to <=20.0 x ULN	0	0.0
	>20.0 x ULN	0	0.0
	Missing	2	
Bilirubin			
	<=ULN (normal)	682	333.34
	>ULN to <=1.5 x ULN	14	5.55
	>1.5 to <=3.0 x ULN	0	0.0
	>3.0 to <=10.0 x ULN	3	2.10
	>10.0 x ULN	1	0.72
	Missing	130	
Alkaline phosphatase			
	<=ULN (normal)	676	394.28
	>ULN to <=2.5 x ULN	151	88.87
	>2.5 to <=5.0 x ULN	1	0.49
	>5.0 to <=20.0 x ULN	1	0.49
	>20.0 x ULN	0	0.0
	Missing	1	
Renal impairment		(n=1158)	
	Mild (CrCl>50 to <80 mL/min)	427	259.09
	Moderate (CrCl>30 to <=50 mL/min)	186	114.99
	Severe (CrCl<=30 mL/min)	12	6.31
	Missing or Other[b]	533	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CrCl=creatinine clearance; N/n=number; ULN=upper limit of normal; x=times
Person-months may be underestimated due to missing exposure data.
[a] Of the 1,207 patients in the Surgery dataset, 830 patients had data measuring hepatic impairment. For each parameter measured, some patients did not have data available and are counted as missing.
[b] Of the 1,158 patients with CrCl data, only 625 patients were categorized as mild, moderate, or severe with respect to renal impairment. The remaining 533 patients were normal or missing baseline CrCl.
Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, PR97-19-002 (spine)

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INDICATION: MDS			
Population	Category at Baseline	Persons	Person-months
Total		(N=102)	
Hepatic Impairment		(n=99)	
ALT			
	<=ULN (normal)	88	607.47
	>ULN to <=2.5 x ULN	8	37.65
	>2.5 to <=5.0 x ULN	2	9.00
	>5.0 to <=20.0 x ULN	1	5.32
	>20.0 x ULN	0	0.0
	Missing	0	
AST			
	<=ULN (normal)	86	585.82
	>ULN to <=2.5 x ULN	8	36.44
	>2.5 to <=5.0 x ULN	5	37.19
	>5.0 to <=20.0 x ULN	0	0.0
	>20.0 x ULN	0	0.0
	Missing	0	
Bilirubin			
	<=ULN (normal)	14	66.76
	>ULN to <=1.5 x ULN	1	1.64
	>1.5 to <=3.0 x ULN	1	5.26
	>3.0 to <=10.0 x ULN	0	0.0
	>10.0 x ULN	1	0.23
	Missing	82	
Alkaline phosphatase			
	<=ULN (normal)	87	584.97
	>ULN to <=2.5 x ULN	9	51.98
	>2.5 to <=5.0 x ULN	0	0.0
	>5.0 to <=20.0 x ULN	1	1.64
	>20.0 x ULN	0	0.0
	Missing	2	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; MDS=myelodysplastic syndrome; N/n=number; ULN=upper limit of normal; x=times
Of the 102 patients in the MDS dataset, 99 patients had data at least one non-missing hepatic ALT, AST, bilirubin, or alkaline phosphatase measurement. For each parameter measured, some of the 99 patients did not have data available and are counted as missing.
MDS Trials: EPO-ANE-3018 and EPOANE3021

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Table 10: Exposure by Special Population (Totals); All Randomised Controlled Clinical Trials

		INDICATION:ALL	
Population	Category at Baseline	Persons	Person-months
Total		(N=7595)	
Hepatic Impairment[a]		(n=4949)	
ALT			
	<=ULN (normal)	3871	20120.94
	>ULN to <=2.5 x ULN	590	4117.09
	>2.5 to <=5.0 x ULN	83	499.91
	>5.0 to <=20.0 x ULN	35	210.46
	>20.0 x ULN	10	46.29
	Missing	360	
AST			
	<=ULN (normal)	3989	19206.83
	>ULN to <=2.5 x ULN	743	5109.09
	>2.5 to <=5.0 x ULN	86	557.63
	>5.0 to <=20.0 x ULN	31	172.81
	>20.0 x ULN	8	32.23
	Missing	92	
Bilirubin			
	<=ULN (normal)	4258	22970.09
	>ULN to <=1.5 x ULN	133	847.21
	>1.5 to <=3.0 x ULN	41	194.07
	>3.0 to <=10.0 x ULN	183	725.78
	>10.0 x ULN	38	118.14
	Missing	296	
Alkaline phosphatase			
	<=ULN (normal)	3380	15908.76
	>ULN to <=2.5 x ULN	1067	7231.01
	>2.5 to <=5.0 x ULN	189	1512.67
	>5.0 to <=20.0 x ULN	58	396.12
	>20.0 x ULN	9	39.16
	Missing	246	
Renal impairment		(n=4920)	
	Mild (CrCl>50 to <80 mL/min)	1910	8854.97
	Moderate (CrCl>30 to <=50 mL/min)	565	1937.25
	Severe (CrCl<=30 mL/min)	60	148.99
	Missing or Other[b]	2385	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CrCl=creatinine clearance; N/n=number; ULN=upper limit of normal; x=times;
Person-months may be underestimated due to missing exposure data.
[a] Of the 7,595 patients, 4,949 patients had data measuring hepatic impairment. For each parameter measured, some patients did not have data available and are counted as missing.
For Renal Impairment, only trials associated with the oncology, ABD, and surgery indications are included
[b] Of the 4,920 patients with CrCl data, only 2,535 patients were categorized as mild, moderate, or severe with respect to renal impairment. The remaining 2,385 patients were normal or missing baseline CrCl.
Chronic Renal Failure – Dialysis Studies: EP86-001 (CEO-C01), EP86-004
Chronic Renal Failure – Predialysis Studies: EPO-AUS-14, EPO-CAN-10, EPO-ITA-7, EPOCKD2002, G86-011, H87-054.
Oncology Studies: CISPLATIN (I88-036, OEO-U24, and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20, and OEOU21), NON-CISPLATIN (I88-037, OEO-U22, and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010
ABD Studies: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058
Surgery Studies: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, PR97-19-002 (spine)
MDS Studies: EPO-ANE-3018 and EPOANE3021

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Exposure in All Clinical Trials Including Open Extensions

Exposure to EPREX in all clinical trials is summarised in Tables 11 through 20 for all patients by duration, dose, age and sex, ethnic and racial origin, baseline renal status, and baseline hepatic status.

In the all clinical trials population, the 15,339 EPREX-treated patients received 94,676.17 person-months exposure to EPREX; this represents an increase of 61,092.47 person-months exposure to EPREX compared with the randomised controlled trials population.

In the all clinical trials population of 15,339 EPREX-treated patients:

- There were 94,676.17 person-months exposure to EPREX (Tables 11 and 12)
- A total of 5,844 (38%) patients were men and 9,393 (62%) patients were women (Tables 15 and 16)
- A total of 6,385 (42%) patients were 65 years of age or older, while 2,560 (17%) patients were 75 years of age or older (Tables 15 and 16)
- A majority of patients (10,515 [69%]) were White, while 1,926 (13%) patients were Black, and 1,353 (9%) patients were Asian, Hispanic or Latino, American Indian or Alaska Native, or Other (Tables 17 and 18); data on ethnic and racial origin were missing for 1,545 (10%) patients
- At total of 5,534 (72%) of the 7,683 patients in the cancer, ABD, surgery, or MDS trials captured in the laboratory database had mild (CRCL >50 to <80 mL/min; n= 2,178), moderate (CRCL >30 to ≤50 mL/min; n=658), or severe (CRCL ≤30 mL/min; n=73) renal impairment at baseline (Tables 19 and 20); CRCL data at baseline were missing or noted as normal in the database for 2,625 patients (Note: only trials associated with the cancer, ABD, surgery, and MDS indications were included in this evaluation because CRF was evaluated as a separate indication by itself.)

Table 11: Exposure by Duration; All Clinical Trials Including Open Extension

INDICATION: CHRONIC RENAL FAILURE - DIALYSIS

Duration of Exposure	Persons (N=2046)	Person-months
Cumulative up to 1 month	81	44.32
Cumulative up to 3 months	387	655.44
Cumulative up to 6 months	897	2900.53
Cumulative up to 9 months	1281	5502.09
Cumulative up to 12 months	1409	6827.99
Cumulative up to 18 months	1650	10552.38
Cumulative up to 24 months	2013	18506.22
Missing	33	.

Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004, EPO-CAN-1, EPO-CAN-13, EPO-INT-37, EPO-INT-68, EPO-INT-77, EPO-ITA-2, ZEO-107 (CCP107P108), ZEO-121 (CC2574P121), ZEO-S01 (CCP102P103)

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INDICATION: CHRONIC RENAL FAILURE - PREDIALYSIS

Duration of Exposure	Persons (N=5610)	Person-months
Cumulative up to 1 month	328	159.77
Cumulative up to 3 months	1121	1778.89
Cumulative up to 6 months	3236	9652.86
Cumulative up to 9 months	3815	14204.81
Cumulative up to 12 months	4294	19169.71
Cumulative up to 18 months	4924	28460.19
Cumulative up to 24 months	5380	38000.39
Cumulative up to 36 months	5602	44429.5
Cumulative up to 48 months	5608	44689.08
Missing	2	.

Chronic Renal Failure – Predialysis Trials: CHOIR (PR00-06014), EPOCKD2001, EPOCKD2002, EPO-AKD-3001, EPO-AKD-3002, EPO-AUS-14, EPO-CAN-10, EPO-INT-14, EPO-ITA-7, G86-011, G86-053, G86-125, H87-054, H87-055, N93-063, POWER (PR00-06009), PROMPT (PR01-06021), Q2W INITIATION (PR03-06001), EPO-NED-15

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INDICATION: ONCOLOGY

Duration of Exposure	Persons (N=5827)	Person-months
Cumulative up to 1 month	651	219.56
Cumulative up to 3 months	2448	4166.18
Cumulative up to 6 months	4703	13750.93
Cumulative up to 9 months	5037	16114.69
Cumulative up to 12 months	5261	18569.69
Cumulative up to 18 months	5586	22901.06
Cumulative up to 24 months	5693	25102.46
Cumulative up to 36 months	5774	27406
Cumulative up to 48 months	5810	28890.58
Cumulative up to 60 months	5816	29224.87
Cumulative up to 72 months	5821	29559.2
Cumulative up to 84 months	5822	29634.46
Missing	5	.

Oncology Trials: CISPLATIN (I88-036, OEO-U24, and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20, and OEOU21), NON-CISPLATIN (I88-037, OEO-U22, and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-ANE-4008, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-ANE-3010, EPO-CAN-29

[TSUB011C.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub011c.sas] 09OCT2015, 14:56

INDICATION:AUTOLOGOUS BLOOD DONATION		
Duration of Exposure	Persons (N=402)	Person-months
Cumulative up to 1 month	316	199.49
Cumulative up to 3 months	389	311.36
Cumulative up to 6 months	399	349.6
Cumulative up to 9 months	400	356.04
Cumulative up to 12 months	400	356.04
Cumulative up to 18 months	400	356.04
Cumulative up to 24 months	400	356.04
Missing	2	.
ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058		
[TSUB011D.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub011d.sas] 09OCT2015, 14:57		

INDICATION: SURGERY		
Duration of Exposure	Persons (N=1352)	Person-months
Cumulative up to 1 month	1251	725.06
Cumulative up to 3 months	1309	805.49
Cumulative up to 6 months	1311	812.78
Cumulative up to 9 months	1311	812.78
Cumulative up to 12 months	1311	812.78
Cumulative up to 18 months	1311	812.78
Cumulative up to 24 months	1311	812.78
Missing	41	.
Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, N93-057, PR97-19-002 (spine)		
[TSUB011E.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub011e.sas] 09OCT2015, 14:59		

INDICATION: MDS		
Duration of Exposure	Persons (N=102)	Person-months
Cumulative up to 1 month	6	2.37
Cumulative up to 3 months	18	27.53
Cumulative up to 6 months	60	247.39
Cumulative up to 9 months	67	297.3
Cumulative up to 12 months	102	677.59
Cumulative up to 18 months	102	677.59
Cumulative up to 24 months	102	677.59
MDS Trials: EPO-ANE-3018 and EPOANE3021		
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Table 12: Exposure by Duration (Totals); All Clinical Trials Including Open Extension

INDICATION: ALL

Duration of Exposure	Persons (N=15339)	Person-months
Cumulative up to 1 month	2633	1350.57
Cumulative up to 3 months	5672	7744.89
Cumulative up to 6 months	10606	27714.1
Cumulative up to 9 months	11911	37287.72
Cumulative up to 12 months	12777	46413.8
Cumulative up to 18 months	13973	63760.03
Cumulative up to 24 months	14899	83455.47
Cumulative up to 36 months	15202	92188.12
Cumulative up to 48 months	15244	93932.29
Cumulative up to 60 months	15250	94266.58
Cumulative up to 72 months	15255	94600.9
Cumulative up to 84 months	15256	94676.17
Missing	83	.

Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004, EPO-CAN-1, EPO-CAN-13, EPO-INT-37, EPO-INT-68, EPO-INT-77, EPO-ITA-2, ZEO-107 (CCP107P108), ZEO-121 (CC2574P121), ZEO-S01 (CCP102P103)
Chronic Renal Failure – Predialysis Trials: CHOIR (PR00-06014), EPOCKD2001, EPOCKD2002, EPO-AKD-3001, EPO-AKD-3002, EPO-AUS-14, EPO-CAN-10, EPO-INT-14, EPO-ITA-7, G86-011, G86-053, G86-125, H87-054, H87-055, N93-063, POWER (PR00-06009), PROMPT (PR01-06021), Q2W INITIATION (PR03-06001), EPO-NED-15.
Oncology Trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20 and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-ANE-4008, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010
ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058
Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, N93-057, PR97-19-002 (spine)
MDS Trials: EPO-ANE-3018 and EPOANE3021

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Table 13: Exposure by Dose; All Clinical Trials Including Open Extension

INDICATION: CHRONIC RENAL FAILURE - DIALYSIS

Initial dose level	Persons (N=2046)	Person-months
10-50 IU/kg QW	170	448.39
51-200 IU/kg QW	13	21.19
1-50 IU/kg TIW	50	264.05
51-100 IU/kg TIW	215	776.05
500-5,000 IU BIW	114	601.4
5,001-10,000 IU BIW	94	372.37
500-1,000 IU QW	20	272.82
1,001-5,000 IU QW	483	6508.81
5,001-10,000 IU QW	465	6185.59
10,001-30,000 IU QW	151	1820.16
500-5,000 IU TIW	93	527.87
5,001-15,000 IU TIW	131	527.01
Missing	47	180.5
Total	2046	18506.22

BIW=2 times a week; N=number; QW=once weekly; TIW=3 times a week
NOTE: Thirty-three of the 2,046 patients are missing exposure data and are not included in the calculation of person-months.
Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004, EPO-CAN-1, EPO-CAN-13, EPO-INT-37, EPO-INT-68, EPO-INT-77, EPO-ITA-2, ZEO-107 (CCP107P108), ZEO-121 (CC2574P121), ZEO-S01 (CCP102P103)

[TSUB013A.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub013a.sas] 09OCT2015, 14:59

INDICATION: CHRONIC RENAL FAILURE - PREDIALYSIS

Initial dose level	Persons (N=5610)	Person-months
1-50 IU/kg QW	156	1532.91
51-200 IU/kg QW	99	1056.2

1-50 IU/kg TIW	99	624.66
51-100 IU/kg TIW	172	1365.45
101-300 IU/kg TIW	105	921.79
500-1,000 IU QW	7	44.81
1,001-5,000 IU QW	276	3196.45
5,001-10,000 IU QW	3298	28287.15
10,001-20,000 IU QW	9	71.75
10,000-20,000 IU Q2W	612	3335.33
20,001-40,000 IU Q2W	9	45.34
30,000 IU Q3W	131	389.13
20,000-40,000 IU Q4W	461	2293.09
60,000-80,000 IU Q4W	22	150.14
500-5,000 IU TIW	117	1068.94
5,001-10,000 IU TIW	6	59.43
Missing	31	246.51
Total	5610	44689.08

N=number; QW=once weekly; Q2W=every 2 weeks; Q4W=every 4 weeks; TIW=3 times a week
NOTE: Two of the 5,610 patients are missing exposure data and are not included in the calculation of person-months.
Chronic Renal Failure – Predialysis Trials: CHOIR (PR00-06014), EPOCKD2001, EPOCKD2002, EPO-AKD-3001, EPO-AKD-3002, EPO-AUS-14, EPO-CAN-10, EPO-INT-14, EPO-ITA-7, G86-011, G86-053, G86-125, H87-054, H87-055, N93-063, POWER (PR00-06009), PROMPT (PR01-06021), Q2W INITIATION (PR03-06001), EPO-NED-15

[TSUB013B.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub013b.sas] 09OCT2015, 14:59

INDICATION: ONCOLOGY

Initial dose level	Persons (N=5827)	Person-months
450 IU/kg QW	242	823.49
600 IU/kg QW	228	912.36
100 IU/kg TIW	65	98.76
150 IU/kg TIW	1629	5280.39
300 IU/kg TIW	124	490.18
40,000 IU QW	2437	18699.93
60,000-80,000 IU Q2W	7	26.74
120,000 IU Q3W	4	13.34
4,000-5,000 IU TIW	125	230.31
10,000 IU TIW	964	3057.18
Missing	2	1.77
Total	5827	29634.46

N=number; QW=once weekly; Q2W=once every 2 weeks; Q3W=once every 3 weeks; TIW=3 times a week
NOTE: Five of the 5,827 patients are missing exposure data and are not included in the calculation of person-months.
Oncology Trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20 and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-ANE-4008, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-ANE-3010, EPO-CAN-29

[TSUB013C.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub013c.sas] 09OCT2015, 14:59

INDICATION:AUTOLOGOUS BLOOD DONATION		
Initial dose level	Persons (N=402)	Person-months
150 IU/kg BIW	29	16.76
300 IU/kg BIW	53	32.59
600 IU/kg BIW	177	105.4
300 IU/kg TIW	71	88.71
600 IU/kg TIW	72	112.59
Total	402	356.04

BIW=2 times a week; N-number; TIW=3 times a week
NOTE: Two women (1 in the 18- to 39-year age group and 1 in the 50-to 59-year age group) are missing exposure data and are not included in the calculation of person-months.
ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058

[TSUB013D.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub013d.sas] 09OCT2015, 14:59

INDICATION:SURGERY		
Initial dose level	Persons (N=1352)	Person-months
100 IU/kg QD	172	82.33
150 IU/kg QD	63	16.46
300 IU/kg QD	437	274.89
600 IU/kg QW	414	279.43
40,000 IU QW	241	159.67
Missing	25	.
Total	1352	812.78

N=number; QD=once daily; QW=once weekly
NOTE: Forty-one of the 1,352 patients are missing exposure data and are not included in the calculation of person-months.
Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, N93-057, PR97-19-002 (spine)

[TSUB013E.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub013e.sas] 09OCT2015, 14:59

INDICATION: MDS		
Initial dose level	Persons(N=102)	Person-months
450 IU/kg QW	85	603.7
40,000 IU QW	8	23.39
80,000 IU QW	9	50.5
Total	102	677.59

MDS=myelodysplastic syndrome; N=number; QW=once weekly
MDS Trials: EPO-ANE-3018 and EPOANE3021

[TSUB013G.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub013g.sas] 09OCT2015, 14:59

Table 14: Exposure by Dose (Totals); All Clinical Trials Including Open Extension

	INDICATION:ALL	
Initial dose level	Persons (N=15339)	Person-months
100 IU/kg QD	172	82.33
150 IU/kg QD	63	16.46
300 IU/kg QD	437	274.89
1-50 IU/kg QW	326	1981.31
51-200 IU/kg QW	112	1077.39
450 IU/kg QW	327	1427.19
600 IU/kg QW	642	1191.79
150 IU/kg BIW	29	16.76
300 IU/kg BIW	53	32.59
600 IU/kg BIW	177	105.4
1-50 IU/kg TIW	149	888.71
51-100 IU/kg TIW	452	2240.26
101-300 IU/kg TIW	1929	6781.08
600 IU/kg TIW	72	112.59
500-5,000 IU BIW	114	601.4
5,001-10,000 IU BIW	94	372.37
500-1,000 IU QW	27	317.63
1,001-5,000 IU QW	759	9705.26
5,001-10,000 IU QW	3763	34472.74
10,001-30,000 IU QW	160	1891.91
40,000 IU QW	2686	18882.99
80,000 IU QW	9	50.5
10,000-20,000 IU Q2W	612	3335.33
20,001-40,000 IU Q2W	9	45.34
60,000-80,000 IU Q2W	7	26.74
30,000 IU Q3W	131	389.13
120,000 IU Q3W	4	13.34
20,000-40,000 IU Q4W	461	2293.09
60,000-80,000 IU Q4W	22	150.14
500-5,000 IU TIW	335	1827.12
5,001-15,000 IU TIW	1101	3643.63
Missing	105	428.78
Total	15339	94676.17

ABD=autologous blood donation; BIW=2 times a week; MDS=myelodysplastic syndrome; N=number; QD=once daily; QW=once weekly; Q2W=once every 2 weeks; Q3W=once every 3 weeks; Q4W=once every 4 weeks; TIW=3 times a week
NOTE: Eighty-three of the 15,339 patients are missing exposure data and are not included in the calculation of person-months
Chronic Renal Failure – Dialysis trials: EP86-001 (CEO-C01), EP86-004, EPO-CAN-1, EPO-CAN-13, EPO-INT-37, EPO-INT-68, EPO-INT-77, EPO-ITA-2, ZEO-107 (CCP107P108), ZEO-121 (CC2574P121), ZEO-S01 (CCP102P103)
Chronic Renal Failure – Predialysis trials: CHOIR (PR00-06014), EPOCKD2001, EPOCKD2002, EPO-AKD-3001, EPO-AKD-3002, EPO-AUS-14, EPO-CAN-10, EPO-INT-14, EPO-ITA-7, G86-011, G86-053, G86-125, H87-054, H87-055, N93-063, POWER (PR00-06009), PROMPT (PR01-06021), Q2W INITIATION (PR03-06001), EPO-NED-15
Oncology trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20, and OEOU21), NON-CISPLATIN (I88-037, OEO-U22, and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-ANE-4008, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010
ABD trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058
Surgery trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, N93-057, PR97-19-002 (spine)
MDS trials: EPO-ANE-3018 and EPOANE3021

[TSUB014.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub014.sas] 04FEB2016, 16:26

Table 15: Exposure by Age Group and Gender; All Clinical Trials Including Open Extension

	INDICATION: CHRONIC RENAL FAILURE - DIALYSIS			
	Men		Women	
Age Group	Persons (N=1149)	Person-months	Persons (N=897)	Person-months
<18 years	2	4.21	2	6.47
18 - 39 years	255	2421	187	1390
40 - 49 years	194	1818	142	1337
50 - 59 years	225	2327	183	1662
60 - 64 years	116	1097	91	772.8
65 - 69 years	118	1101	107	1017
70 - 74 years	124	1082	85	746.7
75 - 79 years	78	688.3	67	525.0
80 - 84 years	25	188.0	23	172.1
>=85 years	10	56.51	9	87.00
Missing	2	3.06	1	3.94

NOTE: Thirty-three of the 2,046 patients are missing exposure data and are not included in the calculation of person-months.
Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004, EPO-CAN-1, EPO-CAN-13, EPO-INT-37, EPO-INT-68, EPO-INT-77, EPO-ITA-2, ZEO-107 (CCP107P108), ZEO-121 (CC2574P121), ZEO-S01 (CCP102P103)

[TSUB015A.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub015a.sas] 09OCT2015, 14:59

	INDICATION: Chronic Renal Failure – PREDIALYSIS			
	Men		Women	
Age Group	Persons (N=2503)	Person-months	Persons (N=3107)	Person-months
<18 years	0	0.00	2	10.22
18 - 39 years	134	1042	210	1742
40 - 49 years	197	1684	272	2266
50 - 59 years	400	3048	522	3982
60 - 64 years	305	2386	379	3396
65 - 69 years	360	2631	397	3517
70 - 74 years	385	3189	441	3513
75 - 79 years	331	2696	373	2853
80 - 84 years	215	1588	285	2351
>=85 years	176	1313	225	1481
Missing	0	0.00	1	0.03

NOTE: Two of the 5,610 patients are missing exposure data and are not included in the calculation of person-months.
Chronic Renal Failure – Predialysis Trials: CHOIR (PR00-06014), EPOCKD2001, EPOCKD2002, EPO-AKD-3001, EPO-AKD-3002, EPO-AUS-14, EPO-CAN-10, EPO-INT-14, EPO-ITA-7, G86-011, G86-053, G86-125, H87-054, H87-055, N93-063, POWER (PR00-06009), PROMPT (PR01-06021), Q2W INITIATION (PR03-06001), EPO-NED-15

[TSUB015B.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub015b.sas] 09OCT2015, 14:59

	INDICATION: ONCOLOGY			
	Men		Women	
Age Group	Persons (N=1671)	Person-months	Persons (N=4156)	Person-months
<18 years	137	561.1	107	581.4
18 - 39 years	48	162.7	438	2793
40 - 49 years	146	423.5	916	5519
50 - 59 years	352	1066	1266	8055
60 - 64 years	271	823.4	557	3379
65 - 69 years	302	935.8	382	2033
70 - 74 years	239	720.8	308	1349
75 - 79 years	120	320.9	132	606.7
80 - 84 years	41	116.2	37	132.4
>=85 years	15	26.38	13	29.37
Missing	0	0.00	0	0.00

NOTE: Five of the 5,827 patients are missing exposure data and are not included in the calculation of person-months.
Oncology Trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20, and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-ANE-4008, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-ANE-3010, EPO-CAN-29

[TSUB015C.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub015c.sas] 09OCT2015, 14:59

	INDICATION:AUTOLOGOUS BLOOD DONATION			
	Men		Women	
Age Group	Persons (N=143)	Person-months	Persons (N=259)	Person-months
<18 years	3	1.77	3	1.84
18 - 39 years	24	27.66	28	29.21
40 - 49 years	20	21.88	21	19.02
50 - 59 years	35	39.29	63	62.29
60 - 64 years	27	23.23	43	36.47
65 - 69 years	15	11.33	42	29.27
70 - 74 years	14	8.97	33	24.54
75 - 79 years	3	1.77	17	10.71
80 - 84 years	2	1.22	8	4.90
>=85 years	0	0.00	1	0.66
Missing	0	0.00	0	0.00

NOTE: Two women (1 in the 18- to 39-year age group and 1 in the 50- to 59-year age group) are missing exposure data and are not included in the calculation of person-months
ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058

[TSUB015D.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub015d.sas] 09OCT2015, 14:59

	INDICATION: SURGERY			
	Men		Women	
Age Group	Persons (N=378)	Person-months	Persons (N=974)	Person-months
<18 years	0	-	0	-
18 - 39 years	24	16.66	52	32.13
40 - 49 years	34	16.95	88	58.81
50 - 59 years	68	30.39	159	101.7
60 - 64 years	65	29.70	123	81.28
65 - 69 years	75	38.34	157	99.29
70 - 74 years	41	25.66	161	94.52
75 - 79 years	43	25.17	130	84.24
80 - 84 years	21	12.39	77	45.57
>=85 years	6	3.58	27	16.43
Missing	1	0.00	0	0.00

NOTE: Forty-one of the 1,352 patients are missing exposure data and are not included in the calculation of person-months.
Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, N93-057, PR97-19-002 (spine)

[TSUB015E.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub015e.sas] 09OCT2015, 14:59

	INDICATION: MDS			
	Men		Women	
Age Group	Persons (N=63)	Person-months	Persons (N=39)	Person-months
<18 years	0	-	0	-
18 - 39 years	0	-	0	-
40 - 49 years	1	1.64	1	5.49
50 - 59 years	3	10.48	1	8.34
60 - 64 years	4	24.41	3	22.14
65 - 69 years	8	59.47	4	22.77
70 - 74 years	15	102.18	12	76.32
75 - 79 years	16	103.98	7	53.16
80 - 84 years	8	52.01	8	65.12
>=85 years	8	42.35	3	27.73
Missing	0	0.00	0	0.00

MDS Trials: EPO-ANE-3018 and EPOANE3021

[TSUB015G.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub015g.sas] 09OCT2015, 15:00

Table 16: Exposure by Age Group and Gender (Totals); All Clinical Trials Including Open Extension

	INDICATION: ALL			
	Men		Women	
Age Group	Persons (N=5907)	Person-months	Persons (N=9432)	Person-months
<18 years	142	567.10	114	599.95
18 - 39 years	485	3669.78	915	5986.53
40 - 49 years	592	3965.40	1440	9205.85
50 - 59 years	1083	6521.07	2194	13871.24
60 - 64 years	788	4383.28	1196	7688.15
65 - 69 years	878	4777.46	1089	6718.85
70 - 74 years	818	5128.71	1040	5803.40
75 - 79 years	591	3836.29	726	4132.73
80 - 84 years	312	1957.95	438	2771.02
>=85 years	215	1442.04	278	1642.35
Missing	3	3.06	2	3.98

NOTE: Eighty-three of the 15,339 patients are missing exposure data and are not included in the calculation of person-months.
Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004, EPO-CAN-1, EPO-CAN-13, EPO-INT-37, EPO-INT-68, EPO-INT-77, EPO-ITA-2, ZEO-107 (CCP107P108), ZEO-121 (CC2574P121), ZEO-S01 (CCP102P103)
Chronic Renal Failure – Predialysis Trials: CHOIR (PR00-06014), EPOCKD2001, EPOCKD2002, EPO-AKD-3001, EPO-AKD-3002, EPO-AUS-14, EPO-CAN-10, EPO-INT-14, EPO-ITA-7, G86-011, G86-053, G86-125, H87-054, H87-055, N93-063, POWER (PR00-06009), PROMPT (PR01-06021), Q2W INITIATION (PR03-06001), EPO-NED-15.
Oncology Trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20, and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-ANE-4008, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010
ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058
Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, N93-057, PR97-19-002 (spine)
MDS Trials: EPO-ANE-3018 and EPOANE3021

[TSUB016.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub016.sas] 09OCT2015, 15:00

Table 17: Exposure by Ethnic and Racial Origin; All Clinical Trials Including Open Extension

INDICATION: CHRONIC RENAL FAILURE - DIALYSIS		
Race	Persons (N=2046)	Person-months
White	1800	16205.50
Black or African American	68	862.03
Asian	75	711.36
American Indian or Alaska Native	6	89.53
Hispanic or Latino	7	89.79
Other [a]	90	548.01
Missing	0	0.00
Total	2046	18506.22

[a] Other races include ABORIGINAL (2), ARABIAN (1), E. INDIAN (1), EAST-INDIAN (4), FILIPINO (2), GYPSY (1), JAMAICAN (1), LEBANESE (1), MAGHREB (1), MACHREB (1), MAGHREBIN (1), MAROCCAN (1), MARTINIQUAISE (1), METIS (1), NATIVE CANADIAN (1), PAKISTANI (1), PORTUGUESE (2), TURC (1), TURKISCH (1), VIETNAMESE (1), WESTINDIAN (1) and MISSING (63).
NOTE: Thirty-three of the 2,046 patients are missing exposure data and are not included in the calculation of person-months.
Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004, EPO-CAN-1, EPO-CAN-13, EPO-INT-37, EPO-INT-68, EPO-INT-77, EPO-ITA-2, ZEO-107 (CCP107P108), ZEO-121 (CC2574P121), ZEO-S01 (CCP102P103)

[TSUB017A.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub017a.sas] 09OCT2015, 15:00

INDICATION: CHRONIC RENAL FAILURE - PREDIALYSIS		
Race	Persons (N=5610)	Person-months
White	3406	27622.60
Black or African American	1516	11805.34

Asian	151	1074.33
American Indian or Alaska Native	15	120.28
Hispanic or Latino	459	3649.64
Other [a]	63	416.89
Missing	0	0.00
Total	5610	44689.08

[a] Other races include ABORIGINAL (1), AFRICAN AMERICAN/ARABIC (1), ARABIC (1), ARMENIAN (1), ARMENIAN ASYRIAN (1), ASIAN/CAUCASIAN (1), BRAZILIAN (1), BROWN (1), COOK ISLAND (2), CUMBODIAN (1), EAST-INDIAN (3), GUYANESE (1), INDIAN (4), INDIAN (EGYPTIAN) (1), JORDANIAN (1), MAORI (3), MIDDLE EASTERN (1), NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER (1), NATIVE HAWAIIAN OR PACIFIC ISLANDER (2), PALASTINIAN (1), PHILIPINO (2), PHILLIPANO (1), PHILLIPINO (1), PORTUGESE (1), RUSSIAN (3), SAMOAN (1), SAMON (1) and MISSING (24).
NOTE: Two of the 5,610 patients are missing exposure data and are not included in the calculation of person-months.
Chronic Renal Failure – Predialysis Trials: CHOIR (PR00-06014), EPOCKD2001, EPOCKD2002, EPO-AKD-3001, EPO-AKD-3002, EPO-AUS-14, EPO-CAN-10, EPO-INT-14, EPO-ITA-7, G86-011, G86-053, G86-125, H87-054, H87-055, N93-063, POWER (PR00-06009), PROMPT (PR01-06021), Q2W INITIATION (PR03-06001), EPO-NED-15

[TSUB017B.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub017b.sas] 09OCT2015, 15:00

INDICATION: ONCOLOGY

Race	Persons (N=5827)	Person-months
White	3772	19561.03
Black or African American	145	430.42
Asian	366	4397.96
American Indian or Alaska Native	3	6.37
Hispanic or Latino	29	100.47
Other [a]	52	487.36
Missing	1460	4650.84
Total	5827	29634.46

[a] Other races include AFGHAN(1), ANTILLEAN(2), ARAB(1), ASIAN-FILIPINO(2), CARIBBEAN (1), COLOURED(2), EAST-INDIAN(3), EGYPTIAN(1), FIJIAN(1), FIRST NATIONS (NATIVE)(1), GUATEMALAN(1), GYPSY(2), HALF-CASTE(3), HISPANIC(12), INDIAN(1), MESTIZA(1), MIXED RACE(3), MIXED- ASIAN/AFRICAN(1), MOTHER-ASIAN/FATHER CAUCASIAN(1), NATIVE HAWAIIAN(1), PHILIPINO(1), PORTUGESE(1), SURINAM(1), TRINIDADIAN(1) and MISSING (7).
NOTE: Five of the 5,827 patients are missing exposure data and are not included in the calculation of person-months.
Oncology Trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20, and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-ANE-4008, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-ANE-3010, EPO-CAN-29

[TSUB017C.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub017c.sas] 09OCT2015, 15:00

INDICATION:AUTOLOGOUS BLOOD DONATION

Race	Persons(N=402)	Person-months
White	372	338.07
Black or African American	24	14.29
Asian	0	0.00
American Indian or Alaska Native	0	0.00
Hispanic or Latino	0	0.00
Other [a]	6	3.68
Missing	0	0.00
Total	402	356.04

[a] Other races include INDIAN (1) and MISSING (5).
NOTE: Two women (1 in the 18- to 39-year age group and 1 in the 50- to 59-year age group) are missing exposure data and are not included in the calculation of person-months.
ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058

[TSUB017D.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub017d.sas] 09OCT2015, 15:00

INDICATION:SURGERY		
Race	Persons (N=1352)	Person-months
White	1148	695.89
Black or African American	173	100.86
Asian	5	1.91
American Indian or Alaska Native	0	0.00
Hispanic or Latino	15	9.30
Other [a]	11	4.83
Missing	0	0.00
Total	1352	812.78

[a] Other races include CAPE VERDIAN (1) and MISSING (10).
NOTE: Forty-one of the 1,352 patients are missing exposure data and are not included in the calculation of person-months.
Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, N93-057, PR97-19-002 (spine)

[TSUB017E.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub017e.sas] 09OCT2015, 15:00

INDICATION: MDS		
Race	Persons (N=102)	Person-months
White	17	73.89
Black or African American	0	0.00
Asian	0	0.00
American Indian or Alaska Native	0	0.00
Hispanic or Latino	0	0.00
Other	0	0.00
Missing	85	603.70
Total	102	677.59

MDS Trials: EPO-ANE-3018 and EPOANE3021

[TSUB017G.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub017g.sas] 09OCT2015, 15:00

Table 18: Exposure by Ethnic and Racial Origin (Totals); All Clinical Trials Including Open Extension

	INDICATION:ALL	
Race	Persons (N=15339)	Person-months
White	10515	64496.99
Black or African American	1926	13212.94
Asian	597	6185.56
American Indian or Alaska Native	24	216.18
Hispanic or Latino	510	3849.20
Other	222	1460.76
Missing	1545	5254.54
Total	15339	94676.17

NOTE: Eight-three of the 15,339 patients are missing exposure data and are not included in the calculation of person-months.
Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004, EPO-CAN-1, EPO-CAN-13, EPO-INT-37, EPO-INT-68, EPO-INT-77, EPO-ITA-2, ZEO-107 (CCP107P108), ZEO-121 (CC2574P121), ZEO-S01 (CCP102P103)
Chronic Renal Failure – Predialysis Trials: CHOIR (PR00-06014), EPOCKD2001, EPOCKD2002, EPO-AKD-3001, EPO-AKD-3002, EPO-AUS-14, EPO-CAN-10, EPO-INT-14, EPO-ITA-7, G86-011, G86-053, G86-125, H87-054, H87-055, N93-063, POWER (PR00-06009), PROMPT (PR01-06021), Q2W INITIATION (PR03-06001), EPO-NED-15.
Oncology Trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20, and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-ANE-4008, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010
ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058
Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, N93-057, PR97-19-002 (spine)
MDS Trials: EPO-ANE-3018 and EPOANE3021

[TSUB018.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub018.sas] 09OCT2015, 15:00

Table 19: Exposure by Special Population; All Clinical Trials Including Open Extension

INDICATION: CHRONIC RENAL FAILURE - DIALYSIS

Population	Category at Baseline	Persons	Person-months
Total		(N=2046)	
Hepatic Impairment		(n=907)	
ALT			
	<=ULN (normal)	718	10836.83
	>ULN to <=2.5 x ULN	27	295.43
	>2.5 to <=5.0 x ULN	5	62.29
	>5.0 to <=20.0 x ULN	1	6.01
	>20.0 x ULN	0	0.0
	Missing	156	
AST			
	<=ULN (normal)	734	10955.04
	>ULN to <=2.5 x ULN	20	242.86
	>2.5 to <=5.0 x ULN	3	34.20
	>5.0 to <=20.0 x ULN	0	0.0
	>20.0 x ULN	0	0.0
	Missing	150	
Bilirubin			
	<=ULN (normal)	754	11215.24
	>ULN to <=1.5 x ULN	1	14.75
	>1.5 to <=3.0 x ULN	1	1.68
	>3.0 to <=10.0 x ULN	0	0.0
	>10.0 x ULN	0	0.0
	Missing	151	
Alkaline phosphatase			
	<=ULN (normal)	251	2705.87
	>ULN to <=2.5 x ULN	59	642.96
	>2.5 to <=5.0 x ULN	7	63.93
	>5.0 to <=20.0 x ULN	1	6.08
	>20.0 x ULN	0	0.0
	Missing	589	

ALT=alanine aminotransfersase; AST=aspartate aminotransferase; ULN=upper limit of normal; x=times
Person-months may be underestimated due to missing exposure data.
Of 2,046 patients in the Chronic Renal Failure – Adult Haemodialysis dataset, 907 patients had at least one non-missing hepatic ALT, AST, BILIRUBIN or alkaline phosphatase measurement. For each parameter measured, some of the 907 patients did not have data available and are counted as missing.
Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004, EPO-CAN-1, EPO-CAN-13, EPO-INT-37, EPO-INT-68, EPO-INT-77, EPO-ITA-2, ZEO-107 (CCP107P108), ZEO-121 (CC2574P121), ZEO-S01 (CCP102P103)

[TSUB019A.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub019a.sas] 09OCT2015, 15:00

INDICATION: CHRONIC RENAL FAILURE - PREDIALYSIS			
Population	Category at Baseline	Persons	Person-months
Total		(N=5610)	
Hepatic Impairment		(n=3796)	
ALT			
	<=ULN (normal)	3652	36913.45
	>ULN to <=2.5 x ULN	108	1330.53
	>2.5 to <=5.0 x ULN	6	60.62
	>5.0 to <=20.0 x ULN	1	21.42
	>20.0 x ULN	0	0.0
	Missing	29	
AST			
	<=ULN (normal)	3580	36016.56
	>ULN to <=2.5 x ULN	135	1622.05
	>2.5 to <=5.0 x ULN	6	59.66
	>5.0 to <=20.0 x ULN	0	0.0
	>20.0 x ULN	0	0.0
	Missing	75	
Bilirubin			
	<=ULN (normal)	3722	38441.00
	>ULN to <=1.5 x ULN	9	70.31
	>1.5 to <=3.0 x ULN	2	7.92
	>3.0 to <=10.0 x ULN	0	0.0
	>10.0 x ULN	0	0.0
	Missing	63	
Alkaline phosphatase			
	<=ULN (normal)	3058	31147.96
	>ULN to <=2.5 x ULN	501	4976.39
	>2.5 to <=5.0 x ULN	15	110.23
	>5.0 to <=20.0 x ULN	3	47.15
	>20.0 x ULN	0	0.0
	Missing	219	

ALT=alanine aminotransfersase; AST=aspartate aminotransferase; ULN=upper limit of normal; x=times
Person-months may be underestimated due to missing exposure data.
Of 5,610 patients in the Chronic Renal Failure – Adult Predialysis dataset, 3,796 patients had at least one non-missing hepatic ALT, AST, BILIRUBIN or alkaline phosphatase measurement. For each parameter measured, some of the 3,796 patients did not have data available and are counted as missing.
Chronic Renal Failure – Predialysis Trials: CHOIR (PR00-06014), EPOCKD2001, EPOCKD2002, EPO-AKD-3001, EPO-AKD-3002, EPO-AUS-14, EPO-CAN-10, EPO-INT-14, EPO-ITA-7, G86-011, G86-053, G86-125, H87-054, H87-055, N93-063, POWER (PR00-06009), PROMPT (PR01-06021), Q2W INITIATION (PR03-06001), EPO-NED-15

[TSUB019B.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub019b.sas] 09OCT2015, 15:00

INDICATION: ONCOLOGY			
Population	Category at Baseline	Persons	Person-months
Total		(N=5827)	
Hepatic Impairment[a]		(n=3496)	
ALT			
	<=ULN (normal)	2760	16974.65
	>ULN to <=2.5 x ULN	522	3986.76
	>2.5 to <=5.0 x ULN	76	479.87
	>5.0 to <=20.0 x ULN	31	198.14
	>20.0 x ULN	10	46.29
	Missing	97	
AST			
	<=ULN (normal)	2640	16135.79
	>ULN to <=2.5 x ULN	680	5052.19
	>2.5 to <=5.0 x ULN	79	513.91
	>5.0 to <=20.0 x ULN	31	172.81
	>20.0 x ULN	8	32.23
	Missing	58	
Bilirubin			
	<=ULN (normal)	3069	19997.21
	>ULN to <=1.5 x ULN	116	843.63
	>1.5 to <=3.0 x ULN	43	202.87
	>3.0 to <=10.0 x ULN	180	723.68
	>10.0 x ULN	36	117.19
	Missing	52	
Alkaline phosphatase			
	<=ULN (normal)	2156	13029.16
	>ULN to <=2.5 x ULN	842	6467.29
	>2.5 to <=5.0 x ULN	196	1516.58
	>5.0 to <=20.0 x ULN	55	387.91
	>20.0 x ULN	9	39.16
	Missing	238	
Renal impairment		(n=3740)	
	Mild (CrCl>50 to <80 mL/min)	1502	9061.75
	Moderate (CrCl>30 to <=50 mL/min)	381	1935.24
	Severe (CrCl<=30 mL/min)	49	159.87
	Missing or Other[b]	1808	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CrCl=creatinine clearance; N/n=number; ULN=upper limit of normal; x=times

Person-months may be underestimated due to missing exposure data.

[a] Of the 5,827 patients in the oncology dataset, 3,496 patients had data measuring hepatic impairment. For each parameter measured, some patients did not have data available and are counted as missing.

[b] Of the 3,740 patients with CrCl data, only 1,932 patients were categorized as mild, moderate, or severe with respect to renal impairment. The remaining 1,808 patients were normal or missing baseline CrCl.

Oncology studies: CISPLATIN (I88-036, OEO-U24, and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20, and OEOU21), NON-CISPLATIN (I88-037, OEO-U22, and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-ANE-4008, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-ANE-3010, EPO-CAN-29

[TSUB019C.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub019c.sas] 19JAN2016, 11:25

INDICATION:AUTOLOGOUS BLOOD DONATION			
Population	Category at Baseline	Persons	Person-months
Total		(N=402)	
Hepatic Impairment[a]		(n=398)	
ALT			
	<=ULN (normal)	367	317.80
	>ULN to <=2.5 x ULN	27	24.05
	>2.5 to <=5.0 x ULN	2	2.56
	>5.0 to <=20.0 x ULN	0	0.0
	>20.0 x ULN	0	0.0
	Missing	2	
AST			
	<=ULN (normal)	378	330.41
	>ULN to <=2.5 x ULN	18	14.00
	>2.5 to <=5.0 x ULN	0	0.0
	>5.0 to <=20.0 x ULN	0	0.0
	>20.0 x ULN	0	0.0
	Missing	2	
Bilirubin			
	<=ULN (normal)	384	326.60
	>ULN to <=1.5 x ULN	9	14.23
	>1.5 to <=3.0 x ULN	0	0.0
	>3.0 to <=10.0 x ULN	0	0.0
	>10.0 x ULN	0	0.0
	Missing	5	
Alkaline phosphatase			
	<=ULN (normal)	367	322.10
	>ULN to <=2.5 x ULN	28	20.53
	>2.5 to <=5.0 x ULN	0	0.0
	>5.0 to <=20.0 x ULN	0	0.0
	>20.0 x ULN	0	0.0
	Missing	3	
Renal impairment		(n=390)	
	Mild (CrCl>50 to <80 mL/min)	141	118.74
	Moderate (CrCl>30 to <=50 mL/min)	40	30.42
	Severe (CrCl<=30 mL/min)	5	3.55
	Missing or Other[b]	204	

ABD=autologous blood donation; ALT=alanine aminotransfersase; AST=aspartate aminotransferase; CrCl=creatinine clearance; ULN=upper limit of normal; x=times
Person-months may be underestimated due to missing exposure data.
[a] Of the 402 patients in the ABD dataset, 398 patients had data measuring hepatic impairment. For each parameter measured, some patients did not have data available and are counted as missing.
[b] Of the 390 patients with CrCl data, only 186 patients were categorized as mild, moderate, or severe with respect to renal impairment. The remaining 204 patients were normal or missing baseline CrCl.
ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058

[TSUB019D.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub019d.sas] 09OCT2015, 15:00

INDICATION:SURGERY			
Population	Category at Baseline	Persons	Person-months
Total		(N=1352)	
Hepatic Impairment[a]		(n=973)	
ALT			
	<=ULN (normal)	658	325.39
	>ULN to <=2.5 x ULN	58	27.86
	>2.5 to <=5.0 x ULN	3	1.25
	>5.0 to <=20.0 x ULN	2	0.99
	>20.0 x ULN	0	0.0
	Missing	252	
AST			
	<=ULN (normal)	887	519.33
	>ULN to <=2.5 x ULN	81	48.85
	>2.5 to <=5.0 x ULN	2	0.53
	>5.0 to <=20.0 x ULN	1	0.49
	>20.0 x ULN	0	0.0
	Missing	2	
Bilirubin			
	<=ULN (normal)	823	417.64
	>ULN to <=1.5 x ULN	16	7.00
	>1.5 to <=3.0 x ULN	0	0.0
	>3.0 to <=10.0 x ULN	3	2.10
	>10.0 x ULN	1	0.72
	Missing	130	
Alkaline phosphatase			
	<=ULN (normal)	799	468.50
	>ULN to <=2.5 x ULN	171	100.40
	>2.5 to <=5.0 x ULN	1	0.49
	>5.0 to <=20.0 x ULN	1	0.49
	>20.0 x ULN	0	0.0
	Missing	1	
Renal impairment		(n=1303)	
	Mild (CrCl>50 to <80 mL/min)	493	299.27
	Moderate (CrCl>30 to <=50 mL/min)	216	132.44
	Severe (CrCl<=30 mL/min)	14	7.52
	Missing or Other[b]	580	

ALT=alanine aminotransfersase; AST=aspartate aminotransferase; CrCl=creatinine clearance; ULN=upper limit of normal; x=times

Person-months may be underestimated due to missing exposure data.

[a] Of the 1,352 patients in the Surgery dataset, 973 patients had data measuring hepatic impairment. For each parameter measured, some patients did not have data available and are counted as missing.

[b] Of the 1,303 patients with CrCl data, only 723 patients were categorized as mild, moderate, or severe with respect to renal impairment. The remaining 580 patients were normal or missing baseline CrCl.

Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, N93-057, PR97-19-002 (spine)

[TSUB019E.rtf] [JNJ-7472179\Z_RMP\RMP_2015\RE_RMP_2015_EU\tsub019e.sas] 09OCT2015, 15:00

INDICATION: MDS			
Population	Category at Baseline	Persons	Person-months
Total		(N=102)	
Hepatic Impairment		(n=99)	
ALT			
	<=ULN (normal)	88	607.47
	>ULN to <=2.5 x ULN	8	37.65
	>2.5 to <=5.0 x ULN	2	9.00
	>5.0 to <=20.0 x ULN	1	5.32
	>20.0 x ULN	0	0.0
	Missing	0	
AST			
	<=ULN (normal)	86	585.82
	>ULN to <=2.5 x ULN	8	36.44
	>2.5 to <=5.0 x ULN	5	37.19
	>5.0 to <=20.0 x ULN	0	0.0
	>20.0 x ULN	0	0.0
	Missing	0	
Bilirubin			
	<=ULN (normal)	14	66.76
	>ULN to <=1.5 x ULN	1	1.64
	>1.5 to <=3.0 x ULN	1	5.26
	>3.0 to <=10.0 x ULN	0	0.0
	>10.0 x ULN	1	0.23
	Missing	82	
Alkaline phosphatase			
	<=ULN (normal)	87	584.97
	>ULN to <=2.5 x ULN	9	51.98
	>2.5 to <=5.0 x ULN	0	0.0
	>5.0 to <=20.0 x ULN	1	1.64
	>20.0 x ULN	0	0.0
	Missing	2	
Renal impairment		(n=101)	
	Mild (CrCl>50 to <80 mL/min)	42	275.12
	Moderate (CrCl>30 to <=50 mL/min)	21	153.33
	Severe (CrCl<=30 mL/min)	5	33.74
	Missing or Other[b]	33	

ALT=alanine aminotransfersase; AST=aspartate aminotransferase; CrCl=creatinine clearance; MDS=myelodysplastic syndrome; ULN=upper limit of normal; x=times
Person-months may be underestimated due to missing exposure data.
[a] Of the 102 patients in the MDS dataset, 99 patients had data measuring hepatic impairment. For each parameter measured, some patients did not have data available and are counted as missing.
[b] Of the 101 patients with CrCl data, only 68 patients were categorized as mild, moderate, or severe with respect to renal impairment. The remaining 33 patients were normal or missing baseline CrCl.
MDS Trials: EPO-ANE-3018 and EPOANE3021
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Table 20: Exposure by Special Population (Totals); All Clinical Trials Including Open Extension

	INDICATION:ALL		
Population	Category at Baseline	Persons	Person-months
Total		(N=15339)	
Hepatic Impairment[a]		(n=9669)	
ALT			
	<=ULN (normal)	8243	65975.59
	>ULN to <=2.5 x ULN	750	5702.28
	>2.5 to <=5.0 x ULN	94	615.59
	>5.0 to <=20.0 x ULN	36	231.89
	>20.0 x ULN	10	46.29
	Missing	536	
AST			
	<=ULN (normal)	8305	64542.95
	>ULN to <=2.5 x ULN	942	7016.38
	>2.5 to <=5.0 x ULN	95	645.49
	>5.0 to <=20.0 x ULN	32	173.31
	>20.0 x ULN	8	32.23
	Missing	287	
Bilirubin			
	<=ULN (normal)	8766	70464.46
	>ULN to <=1.5 x ULN	152	951.56
	>1.5 to <=3.0 x ULN	47	217.72
	>3.0 to <=10.0 x ULN	183	725.78
	>10.0 x ULN	38	118.14
	Missing	483	
Alkaline phosphatase			
	<=ULN (normal)	6718	48258.56
	>ULN to <=2.5 x ULN	1610	12259.55
	>2.5 to <=5.0 x ULN	219	1691.24
	>5.0 to <=20.0 x ULN	61	443.27
	>20.0 x ULN	9	39.16
	Missing	1052	
Renal impairment		(n=5534)	
	Mild (CrCl>50 to <80 mL/min)	2178	9754.87
	Moderate (CrCl>30 to <=50 mL/min)	658	2251.43
	Severe (CrCl<=30 mL/min)	73	204.68
	Missing or Other[b]	2625	

Table 20: Exposure by Special Population (Totals); All Clinical Trials Including Open Extension

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CrCl=creatine clearance; N/n=number; ULN=upper limit of normal; x-times
Person-months may be underestimated due to missing exposure data.
[a] Of the 15,339 patients, 9,669 patients had data measuring hepatic impairment. For each parameter measured, some patients did not have data available and are counted as missing.
For Renal Impairment, only trials associated with oncology, ABD, surgery, and MDS indications are included.
[b] Of the 5,534 patients with CrCl data, only 2,909 patients were categorized as mild, moderate, or severe with respect to renal impairment. The remaining 2,625 patients were normal or missing baseline CrCl.
Chronic Renal Failure – Dialysis Studies: EP86-001 (CEO-C01), EP86-004, EPO-CAN-1, EPO-CAN-13, EPO-INT-37, EPO-INT-68, EPO-INT-77, EPO-ITA-2, ZEO-107 (CCP107P108), ZEO-121 (CC2574P121), ZEO-S01 (CCP102P103)
Chronic Renal Failure – Predialysis Studies: CHOIR (PR00-06014), EPOCKD2001, EPOCKD2002, EPO-AKD-3001, EPO-AKD-3002, EPO-AUS-14, EPO-CAN-10, EPO-INT-14, EPO-ITA-7, G86-011, G86-053, G86-125, H87-054, H87-055, N93-063, POWER (PR00-06009), PROMPT (PR01-06021), Q2W INITIATION (PR03-06001), EPO-NED-15.
Oncology Studies: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20, and OEOU21), NON-CISPLATIN (I88-037, OEO-U22, and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-ANE-4008, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010
ABD Studies: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058
Surgery Studies: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, N93-057, PR97-19-002 (spine)
MDS Studies: EPO-ANE-3018 and EPOANE3021

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

PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

Active substance	Epoetin alfa
Product(s) concerned	EPREX ERYPO ERYPO FS
MAH/MAA name	Janssen-Cilag Pharma GmbH, Austria JANSSEN-CILAG GmbH, Germany Janssen-Cilag NV, Belgium Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag International NV, Cyprus Janssen-Cilag s.r.o., Czech Republic Janssen-Cilag A/S, Denmark Janssen-Cilag OY, Finland JANSSEN-CILAG, France Janssen-Cilag Pharmaceutical S.A.C.I., Greece Janssen-Cilag Limited Janssen-Cilag SpA, Italy Janssen-Cilag, NV, Luxembourg Janssen-Cilag International NV, Malta Janssen-Cilag BV, Netherlands Janssen-Cilag AS, Norway Janssen-Cilag Farmaceutica, Lda, Portugal Janssen-Cilag S.A. Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag S.A., Spain Janssen-Cilag AB, Sweden Janssen-Cilag Ltd, United Kingdom

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Important exclusion criteria that limited the participation of specific subpopulations of patients within the expected target indication across Phase 2/3 clinical trials are listed in Modules SIV.1 and SIV.2. The implications of limited experience with EPREX in populations typically under-represented in the clinical trial development programme(s) with respect to predicting the safety of EPREX in the marketplace are discussed in Module SIV.3.

SIV.1. Limitations of Adverse Drug Reaction Detection Common to All Clinical Trial Development Programmes

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare (it may be appropriate to choose other ADR frequencies)	With an overall exposure to EPREX of an estimated 15,339 patients in the clinical trial programme, rare ADRs (≥1/10,000 and <1/1,000), some of which may be potentially of medical significance, may not have been detected in clinical trials.	Postmarketing surveillance and signal detection are used to detect rare ADRs.
Due to prolonged exposure	Negligible limitations due to the long durations of treatment, especially in the CRF predialysis population with treatment for up to 48 months and exposure of >44,000 person-months. Over 200 patients have been treated in clinical trials for ≥24 months.	There does not appear to be any unknown ADRs due to long-term exposure to EPREX.

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Due to cumulative effects	The half-life of epoetin alfa following multiple doses via IV administration is approximately 4 hours in healthy patients. The half-life for the SC route is estimated to be approximately 24 hours in healthy patients. Patients also produce endogenous erythropoietin that cannot be distinguished from epoetin alfa using standard methods. Therefore, it is difficult to ascertain what constitutes a cumulative effect of exogenous EPREX administration. It is recommended that the dose is titrated according to HGB concentrations, which would minimise the risk of cumulative effects.	No additional adverse cumulative effects have been seen during exposure to EPREX.
Which have a long latency	Studies to evaluate long latency have not been conducted. Therefore, ADRs with long latency may have not been detected.	Postmarketing pharmacovigilance surveillance and signal detection are used to detect events with a long latency.

ADR=adverse drug reaction; CRF=chronic renal failure; HGB=haemoglobin; IV=intravenous; SC=subcutaneous

SIV.2. Effect of Exclusion Criteria in the Clinical Trial Development Plan

Exclusion Criteria That Will Remain as Contraindications

Criteria	Implications for target population
Pure red cell aplasia	Pure red cell aplasia is a very rare and serious condition and was discovered through postauthorisation surveillance. Patients who develop PRCA following treatment with any erythropoietin should not receive EPREX or any other erythropoietin and will have alternative treatment options for anaemia.
Uncontrolled hypertension	Hypertension is the most frequent ADR during treatment with epoetin alfa. Patients with uncontrolled hypertension can experience hypertensive crisis therefore, hypertension should be controlled first before starting treatment with EPREX.
Known hypersensitivity to epoetin alfa or any of its excipients	Patients with known hypersensitivity to epoetin alfa or any of its excipients have alternative treatment options for the treatment of anaemia.
Surgery	
Surgery patients who are unable to receive appropriate antithrombotic therapy during surgery and the postoperative hospital course	Surgery patients who for any reason cannot receive adequate antithrombotic prophylaxis during surgery and the postoperative hospital course will have alternative treatment options for the treatment of anaemia.
Severe cardiac or cerebral disease	Patients with severe cardiac or cerebral disease will have alternative treatment options for the treatment of anaemia.

Exclusion Criteria That are NOT Proposed to Remain as Contraindications

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
Indication: Chronic Renal Failure		
Androgen, corticosteroid, or immunosuppressant therapy	These medications are known to have potential to have an effect on HGB.	These medications were excluded in the early phase of the clinical development programme; however, EPREX is now used in patients who have undergone renal transplantation and are receiving immunosuppressant therapy.
Sickle cell anaemia	Sickle cells cause chronically low RBC production, resulting in anaemia.	Trials have been performed on the efficacy and safety of EPREX for the treatment of anaemia in patients with sickle cell anaemia.
Clinically evident aluminium intoxication	Aluminium intoxication can be caused by dialysis and may lead to aluminium-induced bone disease, microcytic anaemia, and neurologic dysfunction (encephalopathy)	The mechanism of action of EPREX is not considered to increase the severity of aluminium intoxication.
Indication: Cancer		
Pre-trial HGB >10.5 g/dL	No clinically significant effect on reduction of transfusion needs.	Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when HGB concentration is increased beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.
History of seizures	Potential for encephalopathy.	Overall, seizure was reported as an uncommon ADR in EPREX clinical trials. It is recommended that EPREX should be used with caution in patients with epilepsy, history of seizures, or medical conditions associated with a predisposition to seizure activity such as central nervous system infections and brain metastases.

Active infection	It is common clinical practice not to include patients with uncontrolled and potentially life-threatening infections in trials.	The mechanism of action of EPREX is not considered to increase the severity of infections.
Acute blood loss (of any kind)	Needs to be treated by other means; anaemia caused by these events will not benefit from EPREX treatment.	All other causes of anaemia, including blood loss, should be evaluated and treated prior to initiating therapy with epoetin alfa, and when deciding to increase the dose. Treatment with EPREX does not immediately increase HGB in acute situations.
Pregnancy, nursing, or planning a pregnancy (both men and women) within 18 months of enrolment	It is common clinical practice not to include pregnant women in clinical trials.	There are no adequate and well-controlled trials in pregnant women. Findings in animal toxicology studies were interpreted as being secondary to decreased maternal body weight gain when given in weekly doses of approximately 20 times the recommended human dose; therefore, the significance to humans is unknown when given at therapeutic dose levels (see Module SII) It is not known whether exogenous epoetin alfa is excreted in human milk. Epoetin alfa should be used with caution in nursing women. A decision on whether to continue/discontinue breastfeeding or to continue/ discontinue therapy with epoetin alfa should be made taking into account the benefit of breastfeeding to the child and the benefit of epoetin alfa therapy to the woman.

Indication: Surgery

Evidence of haemolysis or gastrointestinal bleeding	Needs to be treated by other means; anaemia caused by these events will not benefit from EPREX treatment.	All other causes of anaemia, including blood loss, should be evaluated and treated prior to initiating therapy with epoetin alfa, and when deciding to increase the dose. Treatment with EPREX does not immediately increase HGB in acute situations.
Active infection	Increased risk of infection in surgery.	The mechanism of action of EPREX is not considered to increase the severity of infections.

ADR=adverse drug reaction; HGB=haemoglobin; PRCA=pure red cell aplasia; RBC=red blood cell

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programme(s)

Children

EPREX is indicated only for the treatment of anaemia associated with CRF in paediatric patients on haemodialysis. A total of 256 children (patients <18 years of age) have been exposed to EPREX in all clinical trials.

Risks associated with use of EPREX in children, including the potential for off-label paediatric use, are discussed in Module SVI.6.2, Potential for Paediatric Off-label Use.

Elderly

Of the 15,339 patients in clinical trials of EPREX (with patient-level data available for this database), 6,384 (42%) were 65 years of age and older, while 2,560 (17%) were 75 years of age and older.

Pregnant or Breastfeeding Women

There are no adequate and well-controlled trials in pregnant women. Findings in animal toxicology studies were interpreted as being secondary to decreased maternal body weight gain when given in weekly doses of approximately 20 times the recommended human dose; therefore, the significance to humans is unknown when given at therapeutic dose levels (see Module SII). It is recommended that epoetin alfa should be used in pregnancy only if the potential benefit outweighs the potential risk to the foetus.

It is not known whether exogenous epoetin alfa is excreted in human milk. Epoetin alfa should be used with caution in nursing women. A decision to continue/discontinue breast-feeding or to continue/discontinue therapy with epoetin alfa should be made taking into account the benefit of breast-feeding to the child and the benefit of epoetin alfa therapy to the woman.

The use of epoetin alfa is not recommended in lactating surgical patients participating in an ABD programme.

Patients with Hepatic Impairment

The safety of epoetin alfa has not been established in patients with hepatic dysfunction. A total of 140 patients known to have hepatic impairment at baseline (alanine aminotransferase >2.5 upper limit of normal [ULN]) were exposed to EPREX in clinical trials. One hundred thirty-five patients with aspartate aminotransferase levels (AST) >2.5 ULN at baseline, 268 patients with bilirubin levels >1.5 ULN at baseline, and 289 patients with alkaline phosphatase levels >2.5 ULN at baseline were exposed to EPREX in clinical trials. No trials have been conducted specifically in patients with hepatic dysfunction.

Patients With Other Relevant Comorbidity

Cardiovascular

Patients with significant cardiovascular comorbidities were excluded in the early (pivotal) trials in the clinical trial programme, but were included in trials conducted afterwards. These post-approval trials contributed significantly to the understanding of the safety profile for the CRF indication; the Correction of Haemoglobin and Outcomes in Renal Insufficiency (CHOIR, PR00-06-014) trial, for example, evaluated 1,432 anaemic patients with CRF. Some of the patients in this trial had comorbidities such as MI, stroke, and CHF hospitalisations. In response to questions from the CHMP, the marketing authorisation holder (MAH) evaluated pooled data from 27 Company-sponsored studies (n=7,254 patients) designed to evaluate efficacy or safety of epoetin alfa treatment in adults with CKD. All analyses were performed both with and without adjustment for baseline risk factors such as comorbidities (including medical history of hypertension, coronary artery disease, heart failure, cerebrovascular disease, and peripheral vascular disease). There were few interactions at the 0.1 level of significance between any HGB or dose variable and the risk factors evaluated, including comorbidities. The sparse occurrence of such interactions, and the lack of any consistency across the outcomes of interest, suggests that the risk factors did not have a noteworthy impact on the effect of mean achieved HGB, cumulative erythropoietin dose, mean achieved HGB/cumulative erythropoietin dose, HGB variation, HGB rate of change, or HGB response on the risks of death, cardiovascular events, cerebrovascular events, or the composite endpoint (CHMP response 2014).

Myeloid Malignancies and Acute Leukaemias

Patients with cancer participating in clinical trials that were part of the preauthorisation cancer clinical programme were anaemic and were receiving an aggressive platinum- or non-platinum-containing chemotherapy regimen. Patients with myeloid malignancies were generally excluded from the trials and therefore data are unavailable. There is currently 1 randomised, double-blind, placebo-controlled trial has been conducted (EPOANE3021) in 130 anaemic patients with MDS.

Immunocompromised Including Transplant Patients

Renal transplant patients receiving immunosuppressive therapy have been treated with EPREX in clinical trials.

Patients with a Disease Severity Different From the Inclusion Criteria in the Clinical Trial Population

Not applicable.

Subpopulations Carrying Known and Relevant Polymorphisms

No pharmacokinetic, pharmacodynamic, or pharmacogenomic assessments of the effect of genetic polymorphisms on the metabolism, safety, or efficacy of EPREX have been conducted.

Patients of Different Racial and/or Ethnic Origin

Of the 15,339 patients in clinical trials of EPREX with patient-level data available, 10,515 (69%) were White, 1,926 (13%) were Black or African American, and 1,353 (9%) were Asian, Hispanic or Latino, American Indian or Native Alaskan, or Other. Data on ethnic and racial origin were missing for 1,545 (10%) patients. EPREX has received market authorisation in 95 countries and the cumulative postmarketing exposure to the drug from first product launch in 1988 through 30 June 2015 is 4,575,083 PY. Therefore, the Company believes that there has been sufficient experience in patients of all races and ethnic origins to exclude safety concerns in any particular one.

SIV.4. Conclusions on the Populations Not Studied and Other Limitations of the Clinical Trial Development Programme

The information related to the populations not studied in clinical trials and to the other limitations of the clinical trial development programme has been reviewed. Because of the vast experience with EPREX since 1988 and the exposure in various populations and settings, none of the populations that were not studied or other limitations of the clinical trial development programme were considered to be missing information because of the amount of experience with EPREX over the past 25 years and the exposure in various populations and settings.

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

PART II: SAFETY SPECIFICATION

Module SV: Postauthorisation Experience

Active substance	Epoetin alfa
Product(s) concerned	EPREX ERYPO ERYPO FS
MAH/MAA name	Janssen-Cilag Pharma GmbH, Austria JANSSEN-CILAG GmbH, Germany Janssen-Cilag NV, Belgium Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag International NV, Cyprus Janssen-Cilag s.r.o., Czech Republic Janssen-Cilag A/S, Denmark Janssen-Cilag OY, Finland JANSSEN-CILAG, France Janssen-Cilag Pharmaceutical S.A.C.I., Greece Janssen-Cilag Limited Janssen-Cilag SpA, Italy Janssen-Cilag, NV, Luxembourg Janssen-Cilag International NV, Malta Janssen-Cilag BV, Netherlands Janssen-Cilag AS, Norway Janssen-Cilag Farmaceutica, Lda, Portugal Janssen-Cilag S.A. Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag S.A., Spain Janssen-Cilag AB, Sweden Janssen-Cilag Ltd, United Kingdom

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SV.1. Action Taken by Regulatory Authorities and/or Marketing Authorisation Holders for Safety Reasons

Detailed Description of Action Taken Since Last Update (4 March 2016) to this Module	
Letter to Healthcare Professionals Regarding SCARs	
Background to issue	Severe cutaneous adverse reactions are considered to be a class effect of all epoetins. The reactions have been more severe with long-acting epoetins. The frequency of these severe cutaneous reactions could not be calculated but they occur very rarely. If the patient has developed a severe cutaneous adverse reaction (such as Stevens-Johnson syndrome or TEN), which is considered to be related to the use of an epoetin, the patient must never be given an epoetin again.
Evidence source	Postmarketing spontaneous reports
Action taken	Following a recommendation by the PRAC, the MAHs of epoetin-containing medicinal products distributed a DHPC letter to Healthcare Professionals in the EEA to inform them of the postmarketing spontaneous reports of SCARs, including Stevens-Johnson syndrome and TEN (which can be life-threatening or fatal), which have been reported in association with epoetin treatment. The MAH decided to distribute the DHPC letter also to countries worldwide where epoetin alfa has a marketing authorisation.
Countries affected	Global
Date(s) of action	August 2017
Addition of Hypersensitivity/Anaphylaxis and Seizures to Risk Management Plan	
Background to issue	PRAC outcome of PBRER assessment of 14 April 2016: Update RMP to include hypersensitivity reactions (including anaphylactic reactions) and seizures as important identified risks. Request was made to update important identified risk of “hypertension” to “hypertension/hypertensive crisis” in a subsequent RMS Day 40 Preliminary Variation Assessment Report of 18 September 2017 and teleconference between ANSM and the MAH (on 11 December 2017). Note: Considering the new definition provided by the GVP module V rev 2, the RMS reconsidered the above request and requested the MAH to no longer consider “hypersensitivity/anaphylaxis” and “seizures” as important identified risks for inclusion in the EU RMP on 22nd May 2018. These two risks do not indeed meet the revised criteria for “important identified risks” to be included in the EU RMP as they are well characterized and described in the SmPC, and are not subject to additional pharmacovigilance or risk minimization activities.
Evidence source	Postmarketing spontaneous reports, PRAC PSUR Final Assessment Report (dated 14 April 2016), PRAC PSUR Single Assessment recommendation (also dated 14 April 2016), RMS Day 40 Preliminary Variation Assessment Report of 18 September 2017 for variation II/129, teleconference between ANSM and the MAH (on 11 December 2017), and Final Assessment Report for variation II/129 (received on 22nd May 2018).

Detailed Description of Action Taken Since Last Update (4 March 2016) to this Module	
Action taken	• Following PRAC outcome of PBRER assessment of 14 April 2016, and teleconference with ANSM on 11 December 2017: Submission of a Type II variation and a subsequent (current) update to the RMP. • Following the revised position from the Reference Member State received on 22th May 2018: Submission of a revised RMP to remove "hypersensitivity/anaphylaxis" and "seizures" from the important identified risks.
Countries affected	Countries of the EEA with a valid marketing authorisation for EPREX/ ERYPO.
Date(s) of action	June 2017, January and June 2018
ANSM=L'Agence Nationale de Sécurité du Médicament et des Produits de Santé; DHPC=Dear Healthcare Provider Communication; EEA=European Economic Area; MAH=marketing authorisation holder; PBRER=Periodic Benefit-Risk Evaluation Report; PRAC= Pharmacovigilance Risk Assessment Committee of the European Medicines Agency; PSUR=Periodic Safety Update Report; RMP=risk management plan; RMS=risk management system; SCARs=severe cutaneous adverse reactions; TEN=toxic epidermal necrolysis	

Cumulative List of Significant Actions Taken for Safety Reasons			
Safety Issue Country(ies)	Action taken	Comment	Date(s)
PRCA			
European Union, Iceland, Norway, Australia, and Switzerland	A variation to amend the SmPC was submitted in all member states as of 14 September 2001. On 26 September 2001, the Company issued an advisory letter to all operating companies worldwide requesting that all relevant national marketing authorisations and prescribing information be amended. This followed a number of reported cases of PRCA and erythropoietin Ab production in CRF patients receiving the product. During the EU review process, an USR procedure was implemented to expedite the amendment to the SmPC. The USR procedure was completed on 9 November 2001.	All EU member states as well as Iceland, Norway, Australia, and Switzerland have amended their national labelling (SmPCs) in line with the USR. All other MAH European Regulatory Affairs-supported countries, where epoetin alfa is marketed, have been informed, where regulatory mechanisms exist, of the update, and regulatory actions taken as appropriate. In agreement with the EU Regulatory Authorities, the Company issued DHPC letters in all EU member states as of 19 November 2001. At the same time, the same information was communicated to all other markets in the rest of the world.	USR: 9 Nov 2001 DHPC letters: 19 Nov 2001
Canada	A Dear Doctor Letter was issued on 26 November 2001 and a public advisory was issued on 3 December 2001 regarding reports of PRCA in CRF patients.		Dear Doctor Letter: 26 Nov 2001 Public Advisory: 3 Dec 2001
Switzerland	On 3 May 2002, following a meeting with the MAH, the Swiss Regulatory Authority requested that the MAH issue a DHPC letters to all Swiss physicians providing an update on the reported cases of PRCA.		DHPC letter: 21 May 2002

Cumulative List of Significant Actions Taken for Safety Reasons			
Safety Issue Country(ies)	Action taken	Comment	Date(s)
EU, Australia, Switzerland, Canada	On 27 May 2002, the French Regulatory Authority, in its role as Reference Member State for the product in the European Union, requested that the MAH prepare a proposed DHPC letter that would provide physicians with updates on the prescribing information with respect to PRCA. The MAH provided the proposal on 31 May 2002. The Company's proposal was discussed at the EU CHMP Pharmacovigilance Working Party of 10 to 12 June 2002. Following the meeting, an USR to amend the SmPCs was initiated. The USR was completed on 12 July 2002. In agreement with the EU Regulatory Authorities, the MAH issued DHPC letters in all EU member states as of 17 July 2002.	During this time, the MAH was also in discussion with the Australian, Canadian, and Swiss Regulatory Authorities and DHPC letters were subsequently issued in those countries.	EU USR completed: 12 July 2002 EU DHPC letters circulated: 17 July 2002 Australia DHPC letters: 4 July 2002 Switzerland DHPC letters: 31 July 2002 Canada DHPC letters: 25 June 2002
Singapore Global	The Singapore HSA distributed a DHPC letter concerning the PRCA cluster discovery. The Company, in consultation with the HSA, submitted an update to the local labelling in Singapore restricting the use of EPREX in patients with CRF by contraindicating the SC route of administration (October 2013). This new contraindication was subsequently communicated to healthcare professionals in Singapore via a second DHPC letter from the HSA. Both DHPC letters were shared with worldwide health care authorities for their information.		Singapore: 13 June 2013, 2 October 2013 Global: 20 June 2013, 3 October 2013

Cumulative List of Significant Actions Taken for Safety Reasons			
Safety Issue Country(ies)	Action taken	Comment	Date(s)
Product recall			
Global	On 31 July 2003, the Company initiated a global voluntary and precautionary recall of specified lots of EPREX prefilled syringe products (1,000-, 2,000-, 3,000-, 4,000-, and 10,000-IU presentations) bearing lot numbers beginning with the numeric codes 01 and 02, which were still within their defined expiry date.	This recall extended to the pharmacy level and was based on the identification of small quantities of extractables in the product from the plain rubber stoppers used in the manufacture of the noted presentations.	31 July 2003
Safety in cancer patients			
Australia	On 5 July 2004, all epoetin alfa licence holders in Australia were requested to provide information on "the safety of recombinant erythropoietin products in cancer patients". This information was provided by the Company by the agreed to deadline of 19 July 2004.	The information was requested in preparation for an Australian Drug Evaluation Committee meeting on 12 to 13 August 2004.	19 July 2004
Turkey	The MAH voluntarily withdrew the cancer indication for EPREX.	This was prompted by a request from the Turkish Ministry of Health to update the product labelling with recommendations concerning the use of recombinant erythropoietin in patients with cancer.	April 2005
Turkey	The cancer indication reinstated and approved in Turkey on 16 November 2006.		16 November 2006

Cumulative List of Significant Actions Taken for Safety Reasons			
Safety Issue Country(ies)	Action taken	Comment	Date(s)
Blood clot formation			
Canada	DHPC letters circulated with new safety information regarding blood clot formation in cancer patients treated with epoetin alfa and similar medicines to higher than typical target HGB levels in this population.		DHPC letter: 13 October 2004
Potential tumour proliferation and TVEs			
Canada Brazil Israel Croatia	Four countries issued DHPC letters relating to the safety issues ongoing with respect to ESAs and potential tumour proliferation and TVEs.		Canada: 16 April 2007 Brazil: 23 April 2007 Israel: 10 May 2007 Croatia: 31 May 2007
Australia South Africa	DHPC letters circulated relating to the ongoing safety issues of potential tumour proliferation and TVEs with respect to ESAs.		Australia: 20 August 2007 South Africa: 5 October 2007

Cumulative List of Significant Actions Taken for Safety Reasons			
Safety Issue Country(ies)	Action taken	Comment	Date(s)
Correction of anaemia in cancer patients			
EU	On 26 June 2008, the CHMP recommended updating the product information for epoetin-containing medicines with a new warning for their use in cancer patients stating that blood transfusion should be the preferred method of correcting anaemia in cancer patients with a reasonably long-life expectancy. The EMEA circulated DHPC letters to all EU Competent Authorities for communication nationally.	The recommendations are based on the conclusion of the Scientific Advisory Group-Oncology expert meeting, which took place on 15 May 2008. The CCDS that was updated in June 2007 is currently considered to appropriately address the CHMP recommendations. A variation to reflect these CHMP recommendations in the EU Mutual Recognition Procedure SmPC was approved.	DHPC letters circulated August 2008 EU Mutual Recognition Procedure variation approved 24 April 2009
Impaired survival in women receiving chemotherapy for breast cancer			
Dear Investigator Letter United States	In November 2014, the Company distributed a Dear Investigator Letter to investigators to inform them of the results of Trial EPO-ANE-3010. At that time, the Informed Consent Form for the study was also updated to inform patients of the results of the study, including reconsenting of patients participating in the study.	Trial EPO-ANE-3010 failed statistically to rule out a 15% risk increase in disease progression or death; the observed degree of risk of adverse tumour outcomes was consistent with that observed in other studies described in the product labelling.	Dear Investigator letter distributed in November 2014

Cumulative List of Significant Actions Taken for Safety Reasons			
Safety Issue Country(ies)	Action taken	Comment	Date(s)
Notification of TSI US	On 29 May 2015, the US FDA issued an official communication to Amgen Inc. of a "Notification of TSI" for epoetin alfa (EPOGEN/PROCRIT) regarding increased tumour recurrence and impaired survival with epoetin alfa treatment of anaemia in women receiving chemotherapy for breast cancer (EPO-ANE-3010). The FDA created this new TSI on 26 May 2015 for epoetin alfa (EPOGEN/PROCRIT).		New TSI created by FDA on 26 May 2015 "Notification of TSI" issued on 29 May 2015.
Postauthorisation measures with ESAs			
PRAC Assessment EU	On 12 March 2015, the PRAC issued advice to the CHMP regarding postauthorisation measures with ESAs, based on the outcome of the statistical analysis of clinical trial data in CKD patients on dialysis and not on dialysis.	The PRAC recommendation, which was endorsed by the CHMP, indicated that no new efficacy or safety concerns were identified based on the data reviewed. A HGB target range below 12 g/dL remains adequate but treatment should be more individualised and the lowest effective dose should be used. Caution is warranted with regard to dose escalation in patients with poor initial response to therapy. Sections 4.2 and 4.4 of the SmPC were updated accordingly, and results of the analysis were added to Section 5.1. Consideration was given to issue a DHPC letter but it was decided to use other means of communication to ensure the targeted audience was made aware of the key messages. These means included publication of a key message on the EMA website and the possibility to communicate via EMA links to health care professionals.	PRAC adoption: 12 March 2015

Cumulative List of Significant Actions Taken for Safety Reasons			
Safety Issue Country(ies)	Action taken	Comment	Date(s)
Dear Healthcare Provider Communication Global	In August 2017, the MAH distributed a DHPC letter to investigators to inform them of the postmarketing spontaneous reports of SCARs, including Stevens-Johnson syndrome and TEN (which can be life-threatening or fatal), which have been reported in association with epoetin treatment.	Severe cutaneous adverse reactions are considered to be a class effect of all epoetins. The reactions have been more severe with long-acting epoetins. The frequency of these severe cutaneous reactions could not be calculated but they occur very rarely. If the patient has developed severe cutaneous adverse reactions (such as Stevens-Johnson syndrome or TEN, which are considered to be related to the use of an epoetin), the patient must never be given an epoetin again.	DHPC distributed in August 2017.

Cumulative List of Significant Actions Taken for Safety Reasons			
Safety Issue Country(ies)	Action taken	Comment	Date(s)
PRAC Assessment EU	On 14 April 2016, a request by PRAC to update the RMP with 2 important identified risks, hypersensitivity reactions (including anaphylactic reactions) and seizures was made based on assessment of the PBRER. On 18 September 2017, in a subsequent RMS Day 40 Preliminary Variation Assessment Report and a teleconference between ANSM and the MAH (on 11 December 2017) a request to update the important identified risk of "hypertension" to "hypertension/hypertensive crisis" was made. Note: Considering the new definition provided by the GVP module V rev 2, the RMS reconsidered the above request and requested the MAH to no longer consider "hypersensitivity/anaphylaxis" and "seizures" as important identified risks for inclusion in the EU RMP on 22nd May 2018. These two risks do not indeed meet the revised criteria for "important identified risks" to be included in the EU RMP as they are well characterized and described in the SmPC, and are not subject to additional pharmacovigilance or risk minimization activities.	Epoetin alfa should be used 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. Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have occurred also during epoetin alfa treatment in patients with previously normal or low blood pressure. The occurrence of seizures during epoetin alfa treatment are uncommon. Hypersensitivity reactions, including cases of rash (including urticaria), anaphylactic reactions, and angioneurotic oedema have been reported during epoetin alfa treatment and are uncommon.	PRAC adoption: 14 April 2016

Ab=antibody; ANSM=L'Agence Nationale de Sécurité du Médicament et des Produits de Santé; CCDS=Company Core Data Sheet; CHMP=Committee on Human Medicinal Products; CNS=central nervous system; CRF=chronic renal failure; DHPC=Dear Healthcare Provider Communication; EMA=European Medicines Agency; EMEA=European Medicines Evaluation Agency; ESA=erythropoiesis-stimulating agent; EU=European Union; FDA=Food and Drug Administration; HGB=haemoglobin; HSA=Health Sciences Authority (Singapore); IU=international units; MAH=marketing authorisation holder; PRAC=Pharmacovigilance Risk Assessment Committee; PRCA=pure red cell aplasia; RMP=risk management plan; RMS=risk management system; SC=subcutaneous; SCARs=severe cutaneous adverse reactions; SmPC=Summary of Product Characteristics; TEN=toxic epidermal necrolysis; TSI=Tracked Safety Issue;TVE=thrombotic vascular event; US=United States; USR=urgent safety restriction

SV.2. Nonstudy Postauthorisation Exposure

SV.2.1. Method used to Calculate Exposure

The postmarketing exposure for epoetin alfa was estimated for distinct populations with the following indications:

- Chronic renal failure requiring dialysis
- Chronic renal failure not yet requiring dialysis (predialysis)
- Cancer
- Surgery
- Human immunodeficiency virus infection[2]

Market research data are not available for the ABD or MDS indication.

Estimates of the number of patients and PY of exposure were obtained for each country by year using data from marketing surveys, patient registries, payer databases, and sales data as available. The route of administration (SC versus IV) was also estimated using these same surveys, as available, in specific countries for patients with CRF receiving dialysis and predialysis.

SV.2.2. Exposure

The cumulative epoetin alfa postmarketing exposure from first product launch in 1989 through 31 August 2017 is person-years (PY) (data on postmarketing exposure in the ABD indication are not available). The following tables show worldwide EPREX postauthorisation exposures by year and indication and EPREX postauthorisation exposures by year and route of administration in patients with CRF (data available through August 2017).

[2] While the HIV indication is not approved in the European Union, these exposure data have been included for completeness in this section.

Worldwide Epoetin Alfa Postmarketing Exposures by Time Period and Indication in Person-Years (Cumulative to 31 August 2017)

Indication	1989-2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017 YTD	Cumulative Total[e]
Dialysis[a]	1,711,101	162,929	163,815	159,271	157,496	162,600	166,124	162,597	154,215	148,913	147,957	136,897	134,199	120,281	118,343	73,130	
Nephrology [pre-dialysis]	179,476	10,159	8,439	9,870	32,953	32,795	32,657	32,669	30,527	29,432	28,864	27,483	26,949	25,486	25,477	15,596	
Cancer[b]	94,798	26,026	26,009	26,241	25,675	27,067	26,873	26,681	25,992	25,486	24,466	22,805	21,637	19,261	17,518	10,376	
Surgery[c]	5,147	2,919	3,320	4,177	3,136	3,293	2,920	2,768	2,509	2,393	2,197	1,992	1,939	1,699	1,517	873	
HIV	1,420	4	6	80	0	0	0	0	0	0	0	0	0	0	0	0	
Total[d]	**1,991,942**	**202,038**	**201,590**	**199,640**	**219,260**	**225,755**	**228,573**	**224,715**	**213,243**	**206,225**	**203,484**	**189,177**	**184,724**	**166,727**	**162,855**	**99,976**	

Key: HIV=Human immunodeficiency virus; ICU=Intensive Care Unit; YTD=Year to Date

a: Nephrology indication assumes a 52-week treatment course such that the number of patients is equal numerically to the number of person-years.

b: The assumed duration of treatment for patients with cancer varied by time period within a range of 9 to 13 weeks.

c: The assumed duration of treatment is a 4-week course.

d: Estimates for non-approved indications Hepatitis C and ICU/Critical care are negligible and not included in this table.

e: Figures are presented to the nearest patient-year for each product by time period and indication. If these figures are added up, minor rounding may occur with cumulative totals which were calculated using raw data estimates for exposure.

Worldwide Postmarketing Exposure by Year and Route of Epoetin Alfa Administration Among Patients With Chronic Renal Failure

	1989-2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017 YTD	Cumulative Total
Renal Dialysis																	
IV Exposure (person-years)	57,798	134,396	142,685	132,572	113,589	118,860	118,636	115,441	109,870	106,478	104,820	96,598	94,315	82,720	81,361	50,435	**1,654,799**
SC Exposure (person-years)	132,772	28,533	21,130	26,699	43,907	43,740	47,488	47,156	44,345	42,435	43,137	40,300	39,884	37,561	36,981	22,696	**695,505**
% IV Exposure	30%	82%	87%	83%	72%	73%	71%	71%	71%	72%	71%	71%	70%	69%	69%	69%	**70%**
% SC Exposure	70%	18%	13%	17%	28%	27%	29%	29%	29%	28%	29%	29%	30%	31%	31%	31%	**30%**
Pre-Dialysis Renal Disease																	
IV Exposure (person-years)	114	782	855	551	1,037	943	637	527	448	415	383	298	289	257	294	184	**7,990**
SC Exposure (person-years)	43,033	9,377	7,584	9,320	31,916	31,852	32,019	32,142	30,080	29,017	28,481	27,185	26,660	25,228	25,183	15,412	**402,712**
% IV Exposure	0%	8%	10%	6%	3%	3%	2%	2%	1%	1%	1%	1%	1%	1%	1%	1%	**2%**
% SC Exposure	100%	92%	90%	94%	97%	97%	98%	98%	99%	99%	99%	99%	99%	99%	99%	99%	**98%**

Key: IV=intravenous; SC=subcutaneous; YTD=Year to Date.

Note: Data through 31 August 2017.

Additional Stratifications for Epoetin Alfa

Patient exposure was estimated by calculation from Intercontinental Medical Statistics Multinational Integrated Data Analysis System (IMS MIDAS™) sales data. Estimates of exposure are based upon finished product. Data from IMS MIDAS are available quarterly and prorated as appropriate to fit the time period of interest. Additional stratifications are provided using Intercontinental Medical Statistics (IMS) Health data where possible and appropriate. Market research sources for nonstudy exposure data are unavailable for breakdowns such as: usage in pregnant or breastfeeding women, usage in hepatic impairment population, usage in renal impairment population.

Exposure by Age and Gender Presented as a Percentage of Prescription Sales

Prescription (Rx) sales stratified by age and gender from IMS MIDAS and are presented below (as a percentage of total Rxs) (see the following tables). IMS Health retains age and gender data for only 3 years, so these tabulations are not cumulative.

Further splits such as gender within age group are not provided since it is not appropriate to stratify to this level of detail based on Rx information available from IMS for these subcategories. Prescription units are reported as absolute values.

Postmarketing (Nonstudy) Epoetin Alfa Exposure by Age Group in the European Union (01 April 2014 to 31 March 2017)

	EU[b]
Age Groups (Years)[a]	**(635,447 Rx[c])**
0-17	0.17%
18-35	2.10%
36-64	13.69%
65+	84.04%

Key: EU=European Union
a: Regional Rx data by age are only available for the last 3 years ending March 2017.
b: Data stratified by age are only available in the EU for the following G5 countries: France, Germany, Italy, Spain and United Kingdom.
c: Rx=Prescriptions in (absolute values), includes retail channels.

Postmarketing (Nonstudy) Epoetin Alfa Exposure by Age Group Outside the European Union (01 April 2014 to 31 March 2017)

	Non-EU[b]
Age Groups (Years)[a]	**(2,102,643 Rx[c])**
0-17	4.05%
18-35	1.38%
36-64	22.21%
65+	70.94%
Age Unspecified	1.42%

Key: EU=European Union
a: Regional Rx data by age are only available for the last 3 years ending March 2017.
b: Data stratified by age are only available in the EU for the following countries: Canada and the United States.
c: Rx=Prescriptions in (absolute values), includes retail channels.

Postmarketing (Nonstudy) Epoetin Alfa Exposure by Gender (01 April 2014 to 31 March 2017)

Region	Females[a]	Males[a]	Patient Gender Unidentified[a]
Canada (64,790 Rx[b])	61.04%	38.96%	0.00%
France (8,833 Rx[b])	49.52%	50.48%	0.00%
Germany (15,923 Rx[b])	38.65%	61.35%	0.00%
Italy (493,935 Rx[b])	56.09%	43.91%	0.00%
Spain (112,817 Rx[b])	44.99%	55.01%	0.00%
United Kingdom (3,939 Rx[b])	89.44%	10.56%	0.00%
United States (2,037,853 Rx[b])	53.91%	44.50%	1.59%

a: Regional Rx data by gender are only available for the last 3 years ending March 2017. Data is only available for France, Germany, Italy, Spain, United Kingdom, United States, and Canada.
b: Rx=Prescriptions in (absolute values), includes retail channels.

SV.3. Postauthorisation Use in Populations Not Studied in Clinical Trials

Market research sources for nonstudy postmarketing exposure data were unavailable for breakdowns such as: usage in pregnant or breastfeeding women, usage in the hepatic impairment population, or usage in the renal impairment population.

SV.4. Postauthorisation Off-label Use

Non-EU approved uses outside the setting of Company-sponsored/-supported clinical trials includes treatment of anaemia in adult human immunodeficiency virus (HIV)-infected patients being treated with zidovudine having endogenous erythropoietin levels ≤500 mU/mL (approved in some non-EU jurisdictions) and settings in which an increase in red cell mass is desired, such as MDS, anaemia of acute and chronic disease, anaemia associated with ribavirin and interferon treatment for hepatitis C, and haemoglobinopathies. Exposure information in non-approved uses is limited.

SV.5. Epidemiologic Study Exposure

Details regarding epidemiologic study exposure are provided in the following table. Additional information regarding the Pharmacoepidemiology Registry EPO-ANE-4014 Prospective Immunogenicity Surveillance (PRIMS) registry is provided in Annex 9. An overview of results for Trials EPO-IMU-401, EPO-IMU-402, and EPO-ANE-4014 is provided in Annex 4. Additional information regarding Trial EPOANE4076 is provided in Annex 9.

Study title Study type	Objectives	Population studied (data source and country)	Duration (study period)	Number of persons (in each group or of cases and controls) and person time (if appropriate)	Comment
EPO-IMU-401/402 Prospective, observational cohort	To prospectively monitor the incidence of PRCA among patients with chronic renal disease who are receiving treatment with epoetin alfa or other erythropoietins.	Patients with CRF who were receiving a Company-marketed ESA; later expanded to include all ESAs. Conducted in Australia, Canada, France, and Germany.	Patients were followed for no less than 1 year after enrolment and followed up for 12 months after the last dose.	9,791	Study information in Annex 4
EPO-ANE-4014 non-interventional immunogenicity surveillance registry, prospective cohort design with enrolment of parallel groups	Estimate IR rate of EPO Ab-mediated PRCA SC exposure to PS-80 formulation of EPREX compared with other currently marketed ESA.	Patients were to have documented CRF (any stage) and be receiving or about to receive SC (within 1 month of the date of enrolment) a marketed ESA. Conducted in 16 EU countries plus Norway, Switzerland, and Australia.	Patients who received SC ESAs were followed up quarterly for 3 years.	15,333 patients were enroled: 5,948 patients received EPREX as initial study treatment, 5,974 Aranesp, 3,382 NeoRecormon. 29 patients did not have treatment data available. 9,602 patients completed the registry: 3,753 EPREX, 3,772 Aranesp, 2,077 NeoRecormon.	Study synopsis in Annex 9

Study title Study type	Objectives	Population studied (data source and country)	Duration (study period)	Number of persons (in each group or of cases and controls) and person time (if appropriate)	Comment
EPOANE4076 A prospective, immunogenicity surveillance registry of ESAs with SC exposure in Thailand	Estimate the incidence of anti-human erythropoiesis and anti-erythropoietin PRCA in patients using any ESA by the SC route.	Patients with CRF receiving ESAs. Conducted in Thailand.	Patients were observed for the development of immunogenicity and PRCA for up to 3 years.	4,018 patients were enroled.	Results indicated that 9 cases of erythropoietin Ab-mediated PRCA were reported. All 9 cases received biocopy r-HuEPO products. The IR of erythropoietin Ab-mediated PRCA cases regardless of specific brand was 1.7 cases per 1,000 PY (95% CI: 0.7812, 3.24). The mean duration of ESA exposure in the 9 erythropoietin Ab-mediated PRCA cases was 13.6 months. Bone marrow biopsies were performed and confirmed PRCA in all cases.

Ab=antibody; CI=confidence interval; CRF=chronic renal failure; ESA=erythropoiesis-stimulating agent; EU=European Union; IR=incidence rate; PRCA=pure red cell aplasia; PS-80=polysorbate 80; PY=person-years; r-HuEPO=recombinant human erythropoietin; SC=subcutaneous

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

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Active substance	Epoetin alfa
Product(s) concerned	EPREX ERYPO ERYPO FS
MAH/MAA name	Janssen-Cilag Pharma GmbH, Austria JANSSEN-CILAG GmbH, Germany Janssen-Cilag NV, Belgium Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag International NV, Cyprus Janssen-Cilag s.r.o., Czech Republic Janssen-Cilag A/S, Denmark Janssen-Cilag OY, Finland JANSSEN-CILAG, France Janssen-Cilag Pharmaceutical S.A.C.I., Greece Janssen-Cilag Limited Janssen-Cilag SpA, Italy Janssen-Cilag, NV, Luxembourg Janssen-Cilag International NV, Malta Janssen-Cilag BV, Netherlands Janssen-Cilag AS, Norway Janssen-Cilag Farmaceutica, Lda, Portugal Janssen-Cilag S.A. Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag S.A., Spain Janssen-Cilag AB, Sweden Janssen-Cilag Ltd, United Kingdom

Data lock point for this module	30 June 2015
Version number of RMP when this module was last updated	5.0

Issue Date: 19 June 2018
Version No: 5.4
Supersedes Version: 5.3
Document No.: EDMS-ERI-13292852:1.0

SVI.1. Potential for Harm From Overdose

The therapeutic margin of epoetin alfa is very wide. Overdosage of epoetin alfa may produce effects that are extensions of the pharmacologic effects of the hormone. Phlebotomy may be performed if excessively high HGB levels occur. Additional supportive care should be provided as necessary. There is no risk for intentional overdose.

SVI.2. Potential for Transmission of Infectious Agents

Good Manufacturing Practices are routinely followed by the MAH and EPREX is produced under Good Manufacturing Practices. No potential for transmission of infectious agents with the use of EPREX has been identified. The MAH performs routine pharmacovigilance activities. If transmission of an infectious agent via EPREX is suspected, appropriate investigations will be conducted. In April 1998, upon request from the EU health authorities, the MAH removed human serum albumin from the formulation and replaced it with polysorbate-80 (PS-80) to eliminate potential risks of contamination by viruses or prions.

SVI.3. Potential for Misuse for Illegal Purposes

Erythropoiesis-stimulating agents have the potential for misuse by endurance athletes to increase HGB levels to enhance aerobic power and performance. The Company's Global Medical Safety database is searched for medically confirmed cases received during each Periodic Benefit-Risk Evaluation Report (PBRER)/Periodic Safety Update Report (PSUR) reporting period that meet PSUR reporting criteria and are coded to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms that may involve drug abuse/misuse. No cases reporting drug abuse/misuse for illegal purposes have been received to date. The potential for misuse for illegal purposes is low.

SVI.4. Potential for Medication Errors

Medication errors have been associated with the use of EPREX. These medication errors, such as inappropriate storage (storage at ambient temperature), incorrect dosage (either dose or frequency of administration), or use of expired product, have not resulted in clinically serious sequelae.

SVI.4.1. Description of Medication Errors During the Clinical Trial Programme

The clinical trial programme for EPREX spans back to the 1980s and in many of the older trials, medication errors were not captured as such in the case report forms. Therefore, information about medication errors and corresponding preferred terms in the entire clinical database is very limited. Data are available from 3 large, randomised, controlled trials in which these data were collected (CRF indication: EPO-AKD-3001 and EPO-AKD-3002; cancer indication: EPO-ANE-4008). These trials were reviewed for medication errors involving EPREX and the data are summarised in the following table. Categories of preferred terms evaluated included the administration of incorrect medication, incorrect dosing, incorrect route of administration, or incorrect patient administered dose.

Description of Medication Errors During the Clinical Trial Programme(s)				
Product Name(s) Description of error	Number of occurrences	Analysis of cause	Steps taken to prevent	Comment
Inappropriate schedule of drug administration	1	Dose of EPREX given less than 24 hours apart	Trial monitor reviewed correct scheduling of drug administration	The trial is closed and no further action is needed
Incorrect dose adjustment	27	Reports of EPREX doses not being increased or decreased per the protocol	Trial monitor reviewed correct dosing adjustments	The trial is closed and no further action is needed
Incorrect storage of drug	19	Reports included EPREX temperature excursions. Many reports lacked detailed information and could not be further evaluated	Trial monitor reviewed the need for temperature control	The trial is closed and no further action is needed
Dosing administration error	28	Reports of doses being prescribed and the HCP not giving the prescribed dose. Also reports of dosing of nonstudy drug on non-dosing week	Trial monitor reviewed dosing and protocol requirements with investigator	The trial is closed and no further action is needed
Wrong data provided for dosing	2	Patients weights were incorrectly recorded leading to incorrect dose administered	Trial monitor reviewed need for appropriate weights and calculation of dosing based off of the weight	The trial is closed and no further action is needed

HCP=health care provider; MAH=Market Authorisation Holder

SVI.4.2. Preventive Measures for the Final Product(s) Being Marketed

To prevent medication errors, accidental exposure to the product, and the incorrect route of administration, Section 4.2 of the SmPC clearly states how the drug should be administered. To prevent the use of expired or poor quality drug administration, Section 6.3 of the SmPC clearly states the shelf life of the product and Section 6.4 of the SmPC clearly states how the product should be stored. Section 6.6 of the SmPC describes the special precautions for handling and disposal as well as a statement not to use the product and discard it if the seal is broken. To prevent drug label or name confusion, the SmPC clearly states “epoetin alfa” and provides guidance on appropriate units of drug. Anti-counterfeiting features on the EPREX packaging

include 1) syringe label contains a field with a Janssen varnish spot, and 2) folding box contains a hidden image on one flap.

SVI.4.3. Effect of Device Failure

In August 2013, ANSM recommended that, based on a high number of customer complaints associated with the use of the PROTECS safety device in Canada (since its launch in December 2007), the MAH should clarify if similar product complaints related to the protective needle-guard system had occurred in Europe. The Company identified that the highest category of EPREX customer complaints was related to "needle safety shield issues/device activation". In this situation, the needle safety device can be accidentally activated due to human error while removing the syringe from the blister prior to administration.

In Europe, between January 2008 and October 2013, syringes had been shipped and in that time, there were 891 reports of "device and delivery system issues". It should be noted that the number of complaints have declined each year since 2008 when the PROTECS device was first introduced in Europe. The Company considers the initial increase in complaint rates to be associated with customers being unfamiliar with the PROTECS device and not with a failure of the device itself. However, to aid patients with the appropriate use of the PROTECS device, the Company took a proactive measure to update the Package Leaflet to provide more detailed instructions and an updated diagram of the PROTECS system to ensure patient safety. The Company will continue to monitor device complaints and report in the PBRER/PSUR.

SVI.4.4. Reports of Medication Errors with the Marketed Product(s)

Description of Error	Number of Occurrences	Analysis of Cause	Steps Taken to Prevent	Comment
Accidental Exposure				
Accidental exposure to product	15	Accidental exposure (including ingestion, skin, and/or eye exposure) to patient/HCP or accidental needle stick to the HCP due to leaky syringe, spring/plunger not working, needle-guard malfunction, or bent needle.	Section 4.2 of the SmPC and the Package Leaflet provide information on how the drug should be administered.	No serious events reported.
Drug Administration Error				
Poor quality drug administered	91	The patients received epoetin alfa that was stored at room temperature, frozen, or expired.	Section 6.4 of the SmPC states how the product is to be stored.	Serious unlisted event[b]: Uterine cancer (1). The MAH will continue to monitor reports of medication error.

Description of Error	Number of Occurrences	Analysis of Cause	Steps Taken to Prevent	Comment
Expired product administered	40	Expired drug was administered by either the HCP or the patient	Section 6.3 of the SmPC states the shelf life of the product.	No serious events reported.
Drug administration error	31	Described various errors: administration to the wrong patient, receiving drug stored at room temperature, given via IM route, "partial amount" administered, and cold drug or empty syringe	Section 4.2 of the SmPC clearly defines how the dose is to be taken.	Serious unlisted events[b]: Death (1), Hyperkalaemia (1), and Plasma cell myeloma (1); the MAH will continue to monitor reports of medication error
Incorrect route of drug administration	20	Epoetin alfa was administered via IM, IV (instead of SC), inhalation, oral, "intra-dermal", or through catheter route	Section 4.2 of the SmPC clearly defines how the dose is to be taken.	Serious unlisted event[b:] Hypertension (1). The MAH will continue to monitor reports of medication error.
Treatment noncompliance	4	Reported treatment noncompliance due to fear of needles, patient refusal, or unspecified reason.	Section 4.2 of the SmPC clearly defines how the dose is to be taken.	No serious unlisted events reported.[b]
Drug administered to patient of inappropriate age	2	Epoetin alfa prescribed to female patients aged 1-month-old and 6-months-old, respectively	Sections 4.1 and 4.2 of the SmPC clearly state indication and dose to be taken, respectively.	No serious unlisted events reported[b]
Wrong drug administered	3	Involved administration of epoetin alfa instead of epoetin beta or an unspecified drug	The SmPC clearly states the correct name of drug.	No serious events reported
Drug Dispensing/ Prescribing Error				
Drug prescribing error	55	Prescribed for unapproved indication or patient population (paediatric), or incorrect dose/route/frequency	Sections 4.1 and 4.2 of the SmPC clearly states indication and dose to be taken, respectively.	No serious events reported
Drug dispensing error	16	Involved dispensing of incorrect dose, dose strength 10 times the prescribed dose, expired drug, or	Section 4.2 of the SmPC clearly defines how the dose is to be taken.	No serious unlisted events reported[b]

Description of Error	Number of Occurrences	Analysis of Cause	Steps Taken to Prevent	Comment
		dispensing of wrong drug.		
Inappropriate Schedule of Drug Administration				
Drug dose omission	62	Missed doses due to syringe-/needle-guard defect/malfunction, incorrectly stored drug, wrong dose dispensed, or forgotten	Section 4.2 of the SmPC clearly defines how the dose is to be taken and Section 6.4 of the SmPC states how the product is to be stored.	No serious unlisted events reported.[b]
Inappropriate schedule of drug administration	41	Administration of epoetin alfa at shorter or longer dosing intervals than prescribed	Section 4.2 of the SmPC clearly defines how the dose is to be taken.	Serious unlisted events[a]: Dizziness (1), Malaise (1), Chest discomfort (1), Extramedullary haematopoiesis (1); the MAH will continue to monitor the inappropriate schedule of drug administration
Incorrect Dose Administered				
Incorrect dose administered	46	Involved receiving less or more than the prescribed/ recommended dose	Section 4.2 of the SmPC clearly defines how the dose is to be taken.	Serious unlisted events: Spinal cord compression (1), Extramedullary haemopoiesis (1), Sepsis (1), and Aplasia pure red cell (1); the MAH will continue to monitor the incorrect dose administered
Incorrect Product Storage				
Incorrect product storage	135	Epoetin alfa was stored at room temperature, in the freezer, or was refrigerated at temperature higher/lower than the label recommended	Section 6.4 of the SmPC states how the product is to be stored.	No serious unlisted events reported[b]
Intercepted drug administration error	1	Described a HCP who discovered the wrong dose was dispensed to the patient and did not administer the drug	Section 4.2 of the SmPC clearly defines how the dose is to be taken.	No serious adverse events reported

Description of Error	Number of Occurrences	Analysis of Cause	Steps Taken to Prevent	Comment
Product Label/Name Confusion				
Product label confusion	3	Described prefilled syringes labelled 1,000 IU/0.5 mL which led to unspecified "mistakes", pharmacist ordered epoetin alfa 40,000 IU prefilled syringe 0.75 mL instead of 1.0 mL, and patient did not know how to handle the PROTECS needle	The SmPC provides clear guidance on appropriate units of drug.	No serious adverse event reported
Product name confusion	1	Epoetin alfa was dispensed instead of Enbrel® (etanercept)	The SmPC clearly states epoetin alfa.	No serious adverse events reported
Product Tampering				
Product tampering	1	Epoetin alfa prefilled syringe was not sealed with plastic wrap	Section 6.6 of the SmPC describes instructions for use, handling, and disposal.	No serious adverse event reported
Underdose				
Underdose	35	Most of the cases reported receiving partial dose as a result of syringe/needle issues, while some cases described dropping the syringe during administration, patient not obtaining enough drug, or patient not being aware of the dose increase	Section 4.2 of the SmPC clearly defines how the dose is to be taken.	Serious unlisted events: Sepsis (1), Aplasia pure red cell (1); the MAH will continue to monitor reports of medication error.
Wrong Technique in Drug Usage Process				
Wrong technique in drug usage process	13	Described various circumstances including wrong technique during injection, re-use of syringe, shaking of drug prior to administration, or injecting drug that	Section 4.2 of the SmPC clearly defines how the dose is to be taken and Sections 6.4 and 6.6 of the SmPC define how the product is to be stored.	No serious unlisted events reported[b]

Description of Error	Number of Occurrences	Analysis of Cause	Steps Taken to Prevent	Comment
		was frozen or had air bubbles		
Medication Error (Miscellaneous)				
Medication error	24	Involved various errors that included dispensing the wrong needle guard for the dose, improper storage, HCP ordering the wrong strength concentration, receiving batch number that was not distributed in that country	Section 4.2 of the SmPC clearly defines how the dose is to be taken and Section 6.4 of the SmPC states how the product is to be stored.	Serious unlisted event: Blood pressure abnormal (1), Fall (1); the MAH will continue to monitor reports of medication error.
Circumstance or information capable of leading to medication error	1	Patient received drug from syringe with the PROTECS system	Section 4.2 of the SmPC clearly defines how the dose is to be taken.	No serious adverse events reported.

AE=adverse event; CCDS=Company Core Data Sheet; CT=computerised tomogram; HCP=health care provider; IM=intramuscular; IV=intravenous; MAH=marketing authorisation holder; MDS=myelodysplastic syndrome; MRI=magnetic resonance imaging; SC=subcutaneous; SmPC=Summary of Product Characteristics

a: Number of occurrences is derived from total reported counts for each individual MedDRA preferred term based on Global Medical Safety (GMS) Safety Data Extraction ticket number SDE002650 (dated 13 July 2015).

b: Serious unlisted events (based on the CCDS) were only included if they were temporally associated with medication error and/or an association with the medication error appeared to be plausible.

SVI.5. Potential for Off-label Use

The potential exists that EPREX will be prescribed in a manner that is not consistent with the product label (eg, in patients with a different treatment indication, in a different patient population, or in the administration of the product).

Based on the review of the safety data, there is the potential for EPREX to be used to treat patients with other causes of anaemia and to be prescribed, administered, or used incorrectly. The common off-label uses included the treatment of anaemia associated with haematologic malignancy or anaemia induced by hepatitis C treatment. Approved indications for the product are stated in the SmPC, as well as the dosage and administration recommendations.

SVI.6. Specific Paediatric Issues

SVI.6.1. Issues Identified in Paediatric Investigation Plans

There is no Paediatric Investigational Plan for EPREX.

SVI.6.2. Potential for Paediatric Off-label Use

Section 4.1 of the SmPC states that EPREX is indicated for the treatment of symptomatic anaemia associated with CRF in paediatric patients on haemodialysis. Exposure in non-approved uses is limited.

SVI.7. Conclusions

There are no safety concerns identified from this module.

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

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

Active substance	Epoetin alfa
Product(s) concerned	EPREX ERYPO ERYPO FS
MAH/MAA name	Janssen-Cilag Pharma GmbH, Austria JANSSEN-CILAG GmbH, Germany Janssen-Cilag NV, Belgium Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag International NV, Cyprus Janssen-Cilag s.r.o., Czech Republic Janssen-Cilag A/S, Denmark Janssen-Cilag OY, Finland JANSSEN-CILAG, France Janssen-Cilag Pharmaceutical S.A.C.I., Greece Janssen-Cilag Limited Janssen-Cilag SpA, Italy Janssen-Cilag, NV, Luxembourg Janssen-Cilag International NV, Malta Janssen-Cilag BV, Netherlands Janssen-Cilag AS, Norway Janssen-Cilag Farmaceutica, Lda, Portugal Janssen-Cilag S.A. Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag S.A., Spain Janssen-Cilag AB, Sweden Janssen-Cilag Ltd, United Kingdom

Data lock point for this module	20 December 2017
Version number of RMP when this module was last updated	5.4

Issue Date: 19 June 2018
Version No: 5.4
Supersedes Version: 5.3
Document No.: EDMS-ERI-13292852:1.0

SVII.1. Newly Identified Safety Concerns (since this module was last submitted)

Hypertensive crisis has been added to the Important Identified Risk of Hypertension.

SVII.2. Recent Study Reports With Implications for Safety Concerns

Completed trials from the Postauthorisation Pharmacovigilance Plan are summarised in Section III.5.2.

Trial EPO-ANE-3010 is a randomised, open-label, multicentre, Phase 3 international trial of epoetin alfa plus best standard supportive care versus standard supportive care alone in anaemic patients with metastatic breast cancer receiving standard chemotherapy. Patients were assessed for tumour response during the open-label phase every 8 weeks for 1 year after randomisation or until there was documented progressive disease. After 1 year in the absence of progressive disease, patients were evaluated for tumour response every 12 weeks. Patients continued in the open-label phase until progressive disease was documented or the patient died, even if the patient's chemotherapy was discontinued or changed. Following the documentation of progressive disease, patients entered the long-term follow-up phase, during which time survival status was checked every 3 months until the patient died/withdrew or the trial ended.

A clinical study report (CSR) for Trial EPO-ANE-3010 has been completed given that the number of progression-free survival (PFS) events reached the target of 1,650 events for the analysis of the primary endpoint. A final analysis for survival was performed after 1,650 patients died. As of the clinical cutoff date of 07 July 2014 for the CSR, the median PFS per investigator assessment of disease progression was 7.4 months in each arm (HR 1.09, 95% CI: 0.99, 1.20), indicating that the study objective was not met. Median PFS with disease progression assessed by the Independent Review Committee was 7.6 months in each arm (HR 1.03, 95% CI: 0.92, 1.15). At the time of the clinical cutoff date of 07 July 2014 for the CSR, 1,337 deaths were reported. Median overall survival in the epoetin alfa plus standard-of-care group was 17.2 months compared with 17.4 months in the standard-of-care alone group (HR 1.06, 95% CI: 0.95, 1.18).

SVII.3. Details of Important Identified and Potential Risks From Clinical Development and Postauthorisation Experience (including newly identified)

Important Identified Risks with the use of EPREX are:

- Thrombotic vascular events
- Pure red cell aplasia
- Hypertension/Hypertensive crisis

Important Potential Risks with the use of EPREX are:

- Disease progression
- Survival impact
- Congestive heart failure

Odds ratios and 95% CI for the risk of each adverse event in epoetin alfa-treated patients are also presented in these tables for the randomised trials. A risk was considered statistically significantly higher in the epoetin alfa-treated group than in the control group without epoetin alfa, when the lower boundary of the 95% CI of the ORs was larger than 1.0 (ie, when the 95% CI did not include 1.0). Odds ratios are provided only for the analyses including trials with a control group, as providing ORs for a mixture of trials with control and trials without control is not appropriate and can lead to misinterpretation.

With clinical trial programme experience of over 25 years, data related to severity and outcomes for nonserious adverse events were not collected for a majority of the epoetin alfa trials. The legacy trials did not capture NCI-CTCAE (Common Terminology Criteria for Adverse Events) (CTCAE), formerly called the Common Toxicity Criteria (CTC or NCI CTC) grading. The risk tables present a combination for each risk of the severity grading of mild, moderate, or severe, where applicable, and the toxicity grades (Grades 1 to 4), where applicable.

Therefore, due to the difference in reporting of toxicity grades versus non-toxicity severities, the characterisation of severity and outcomes data are only provided for serious adverse events and a total for all indications per risk is not provided.

The data below came from clinical trials that included both labelled (correction of anaemia) and non-labelled (beyond correction of anaemia) dosage regimens. MedDRA Version 20.0 (the current version at the time of the database lock for this analysis) was used to classify the clinical trials adverse event information that is summarised in this module.

Important Identified Risks

Important Identified Risk - Thrombotic Vascular Events

Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Thromboembolic Vascular Events in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

INDICATION: CHRONIC RENAL FAILURE - DIALYSIS			
	Epoetin alfa (N=2046)	Non-ESA control (N=46)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b]	97	46	
N			
Any Treatment-Emergent Event, n (%)	2 (2.06%)	0 (0.00%)	N/A
Outcome (Based on Serious AEs)	0	0	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	0 (0.00%)	
Recovered	0 (0.00%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Mild	0 (0.00%)	0 (0.00%)	
Moderate	0 (0.00%)	0 (0.00%)	
Severe	1 (1.03%)	0 (0.00%)	
Unknown	1 (1.03%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	
Trials without control [c]	1949	0	
N			
Any Treatment-Emergent Event, n (%)	255 (13.1%)	0 (0.00%)	N/A
Outcome (Based on Serious AEs)	154	0	
Fatal	3 (0.15%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	19 (0.97%)	0 (0.00%)	
Recovered	131 (6.72%)	0 (0.00%)	
N/A	1 (0.05%)	0 (0.00%)	
Severity, n (%)			
Mild	51 (2.62%)	0 (0.00%)	
Moderate	75 (3.85%)	0 (0.00%)	
Severe	129 (6.62%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	
Combined (All Trials)	2046	46	
N			
Any Treatment-Emergent Event, n (%)	257 (12.6%)	0 (0.00%)	
Outcome (Based on Serious AEs)	154	0	
Fatal	3 (0.15%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	19 (0.93%)	0 (0.00%)	
Recovered	131 (6.40%)	0 (0.00%)	
N/A	1 (0.05%)	0 (0.00%)	
Severity, n (%)			
Mild	51 (2.49%)	0 (0.00%)	
Moderate	75 (3.67%)	0 (0.00%)	
Severe	130 (6.35%)	0 (0.00%)	
Unknown	1 (0.05%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	

AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.

[b] Includes EP86-001 (CEO-C01), EP86-004

[c] Includes EPO-CAN-1, EPO-CAN-13, EPO-INT-37, EPO-INT-68, EPO-INT-77, EPO-ITA-2, ZEO-107 (CCP107P108), ZEO-121 (CC2574P121), ZEO-S01 (CCP102P103)

Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004, EPO-CAN-1, EPO-CAN-13, EPO-INT-37, EPO-INT-68, EPO-INT-77, EPO-ITA-2, ZEO-107 (CCP107P108), ZEO-121 (CC2574P121), ZEO-S01 (CCP102P103)

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Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Thromboembolic Vascular Events in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

INDICATION: CHRONIC RENAL FAILURE - PREDIALYSIS			
	Epoetin alfa (N=5610)	Non-ESA control (N=325)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b]	464	325	
N			
Any Treatment-Emergent Event, n (%)	23 (4.96%)	8 (2.46%)	2.26 (0.98,5.24)
Outcome (Based on Serious AEs)	13	3	
Fatal	1 (0.22%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	2 (0.43%)	0 (0.00%)	
Recovered	10 (2.16%)	3 (0.92%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Mild	5 (1.08%)	3 (0.92%)	
Moderate	8 (1.72%)	2 (0.62%)	
Severe	10 (2.16%)	2 (0.62%)	
Unknown	0 (0.00%)	1 (0.31%)	
Missing	0 (0.00%)	0 (0.00%)	
Trials without control [c]	5146	0	
N			
Any Treatment-Emergent Event, n (%)	267 (5.19%)	0 (0.00%)	N/A
Outcome (Based on Serious AEs)	194	0	
Fatal	32 (0.62%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	7 (0.14%)	0 (0.00%)	
Recovered	121 (2.35%)	0 (0.00%)	
N/A	34 (0.66%)	0 (0.00%)	
Severity, n (%)			
Mild	41 (0.80%)	0 (0.00%)	
Moderate	70 (1.36%)	0 (0.00%)	
Severe	138 (2.68%)	0 (0.00%)	
Unknown	18 (0.35%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	
Combined (All Trials)	5610	325	
N			
Any Treatment-Emergent Event, n (%)	290 (5.17%)	8 (2.46%)	
Outcome (Based on Serious AEs)	207	3	
Fatal	33 (0.59%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	9 (0.16%)	0 (0.00%)	
Recovered	131 (2.34%)	3 (0.92%)	
N/A	34 (0.61%)	0 (0.00%)	
Severity, n (%)			
Mild	46 (0.82%)	3 (0.92%)	
Moderate	78 (1.39%)	2 (0.62%)	
Severe	148 (2.64%)	2 (0.62%)	
Unknown	18 (0.32%)	1 (0.31%)	
Missing	0 (0.00%)	0 (0.00%)	

AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.

[b] Includes EPO-AUS-14, EPO-CAN-10, EPO-ITA-7, EPOCKD2002, G86-011, H87-054

[c] Includes CHOIR (PR00-06014), EPOCKD2001, EPO-AKD-3001, EPO-AKD-3002, EPO-INT-14, G86-053, G86-125, H87-055, N93-063, POWER (PR00-06009), PROMPT (PR01-06021), Q2W INITIATION (PR03-06001), EPO-NED-15

Chronic Renal Failure – Predialysis Trials: CHOIR (PR00-06014), EPOCKD2001, EPOCKD2002, EPO-AKD-3001, EPO-AKD-3002, EPO-AUS-14, EPO-CAN-10, EPO-INT-14, EPO-ITA-7, G86-011, G86-053, G86-125, H87-054, H87-055, N93-063, POWER (PR00-06009), PROMPT (PR01-06021), Q2W INITIATION (PR03-06001), EPO-NED-15

Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Thromboembolic Vascular Events in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

	INDICATION: ONCOLOGY		
	Epoetin alfa (N=5827)	Non-ESA control (N=4719)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b]	5323	4719	
N			
Any Treatment-Emergent Event, n (%)	358 (6.73%)	182 (3.86%)	1.88 (1.56,2.27)
Outcome (Based on Serious AEs)	97	41	
Fatal	12 (0.23%)	5 (0.11%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	35 (0.66%)	10 (0.21%)	
Recovered	45 (0.85%)	19 (0.40%)	
N/A	5 (0.09%)	7 (0.15%)	
Severity, n (%)			
Grade=1	39 (0.73%)	25 (0.53%)	
Grade=2	102 (1.92%)	55 (1.17%)	
Grade=3	201 (3.78%)	90 (1.91%)	
Grade>=4	5 (0.09%)	5 (0.11%)	
Unknown	11 (0.21%)	7 (0.15%)	
Trials without control [c]	504	0	
N			
Any Treatment-Emergent Event, n (%)	28 (5.56%)	0 (0.00%)	N/A
Outcome (Based on Serious AEs)	24	0	
Fatal	1 (0.20%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	9 (1.79%)	0 (0.00%)	
Recovered	14 (2.78%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Grade=1	5 (0.99%)	0 (0.00%)	
Grade=2	14 (2.78%)	0 (0.00%)	
Grade=3	8 (1.59%)	0 (0.00%)	
Grade>=4	1 (0.20%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	
Combined (All Trials)	5827	4719	
N			
Any Treatment-Emergent Event, n (%)	386 (6.62%)	182 (3.86%)	
Outcome (Based on Serious AEs)	121	41	
Fatal	13 (0.22%)	5 (0.11%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	44 (0.76%)	10 (0.21%)	
Recovered	59 (1.01%)	19 (0.40%)	
N/A	5 (0.09%)	7 (0.15%)	
Severity, n (%)			
Grade=1	44 (0.76%)	25 (0.53%)	
Grade=2	116 (1.99%)	55 (1.17%)	
Grade=3	209 (3.59%)	90 (1.91%)	
Grade>=4	6 (0.10%)	5 (0.11%)	
Unknown	11 (0.19%)	7 (0.15%)	

AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.

[b] Includes CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20 and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010

[c] Includes EPO-ANE-4008

Oncology Trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20 and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-ANE-4008, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010

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Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Thromboembolic Vascular Events in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

INDICATION:AUTOLOGOUS BLOOD DONATION			
	Epoetin alfa (N=402)	Non-ESA control (N=242)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b]	402	242	
N			
Any Treatment-Emergent Event, n (%)	10 (2.49%)	7 (2.89%)	1.00 (0.38,2.61)
Outcome (Based on Serious AEs)	N/A	N/A	
Severity, n (%)			
Mild	0 (0.00%)	2 (0.83%)	
Moderate	6 (1.49%)	3 (1.24%)	
Severe	4 (1.00%)	1 (0.41%)	
Missing	0 (0.00%)	1 (0.41%)	
Combined (All Trials)	402	242	
N			
Any Treatment-Emergent Event, n (%)	10 (2.49%)	7 (2.89%)	
Outcome (Based on Serious AEs)	N/A	N/A	
Severity, n (%)			
Mild	0 (0.00%)	2 (0.83%)	
Moderate	6 (1.49%)	3 (1.24%)	
Severe	4 (1.00%)	1 (0.41%)	
Missing	0 (0.00%)	1 (0.41%)	

AE=adverse event; ABD=autologous blood donation; CI=confidence interval; ESA=erythropoiesis-stimulating agent; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.

[b] Includes CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058

ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058

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Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Thromboembolic Vascular Events in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

	INDICATION:SURGERY		
	Epoetin alfa (N=1352)	Non-ESA control (N=922)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b]	1207	922	
N			
Any Treatment-Emergent Event, n (%)	75 (6.21%)	35 (3.80%)	1.49 (0.98,2.25)
Outcome (Based on Serious AEs)	18	11	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	5 (0.41%)	1 (0.11%)	
Recovered	12 (0.99%)	8 (0.87%)	
N/A	1 (0.08%)	2 (0.22%)	
Severity, n (%)			
Mild	30 (2.49%)	14 (1.52%)	
Moderate	21 (1.74%)	13 (1.41%)	
Severe	24 (1.99%)	8 (0.87%)	
Unknown	0 (0.00%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	
Trials without control [c]	145	0	
N			
Any Treatment-Emergent Event, n (%)	3 (2.07%)	0 (0.00%)	N/A
Outcome (Based on Serious AEs)	0	0	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	0 (0.00%)	
Recovered	0 (0.00%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Mild	1 (0.69%)	0 (0.00%)	
Moderate	2 (1.38%)	0 (0.00%)	
Severe	0 (0.00%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	
Combined (All Trials)	1352	922	
N			
Any Treatment-Emergent Event, n (%)	78 (5.77%)	35 (3.80%)	
Outcome (Based on Serious AEs)	18	11	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	5 (0.37%)	1 (0.11%)	
Recovered	12 (0.89%)	8 (0.87%)	
N/A	1 (0.07%)	2 (0.22%)	
Severity, n (%)			
Mild	31 (2.29%)	14 (1.52%)	
Moderate	23 (1.70%)	13 (1.41%)	
Severe	24 (1.78%)	8 (0.87%)	
Unknown	0 (0.00%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	

AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.

[b] Includes EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, PR97-19-002 (spine)

[c] Includes N93-057

Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, N93-057, PR97-19-002 (spine)

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Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Thromboembolic Vascular Events in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

INDICATION: MDS			
	Epoetin alfa (N=102)	Non-ESA control (N=53)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b]	102	53	
N			
Any Treatment-Emergent Event, n (%)	2 (1.96%)	0 (0.00%)	N/A
Outcome (Based on Serious AEs)	1	0	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	0 (0.00%)	
Recovered	1 (0.98%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Grade=1	1 (0.98%)	0 (0.00%)	
Grade=2	0 (0.00%)	0 (0.00%)	
Grade=3	1 (0.98%)	0 (0.00%)	
Grade>=4	0 (0.00%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	
Combined (All Trials)	102	53	
N			
Any Treatment-Emergent Event, n (%)	2 (1.96%)	0 (0.00%)	
Outcome (Based on Serious AEs)	1	0	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	0 (0.00%)	
Recovered	1 (0.98%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Grade=1	1 (0.98%)	0 (0.00%)	
Grade=2	0 (0.00%)	0 (0.00%)	
Grade=3	1 (0.98%)	0 (0.00%)	
Grade>=4	0 (0.00%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	

AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; MDS=myelodysplastic syndrome; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.
[b] Includes EPO-ANE-3018 and EPOANE3021

MDS Trials: EPO-ANE-3018 and EPOANE3021

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In 2008, the Company performed an updated analysis of thrombotic vascular events (TVEs) in cancer clinical trials. The analysis included 32 completed, randomised clinical trials of epoetin alfa in patients with cancer, for which patient-level data were then available. These 32 trials, which included a total of 7,444 patients, confirmed the previous analysis using a larger data set. Thrombotic vascular events occurred in 118 (3.5%) of the 3,420 patients in the control group compared with 260 (6.5%) of the 4,024 patients in the epoetin alfa group. The HR was 2.09 (95% CI: 1.67, 2.60) (Company data on file).

Postmarketing Experience:

The cumulative reporting rates for TVEs in the postmarketing setting as of 30 June 2015 are the following, based on a cumulative postmarketing exposure of 4,575,083 PY: for all indications, 10 cases/100,000 PY; for the surgery indication: 126.3 cases/100,000 PY; for the cancer indication: 32.7 cases/100,000 PY, and for the CRF indication: 2.5 cases/100,000 PY.

Nature of Risk:

Chronic Renal Failure

Among the 2,046 patients treated in adult haemodialysis clinical trials with EPREX, there were 257 treatment-emergent TVEs. Of those 257 events, 205 events were considered to be moderate to severe. One hundred fifty-four of the 257 TVE events were reported as serious adverse events. Among the 5,610 patients treated in adult predialysis clinical trials with EPREX, there were 290 treatment-emergent TVEs. Of those 290 events, 226 events were considered to be moderate to severe. Two hundred seven of the 290 TVE events were reported as serious adverse events.

Cancer

There is an increased risk for TVEs among patients with cancer who receive ESAs for the treatment of chemotherapy-induced anaemia (CIA). Among the 5,827 patients treated in cancer clinical trials with EPREX, there were 386 (6.62%) treatment-emergent TVEs. Of those 386 events, 209 (54%) events were considered to be Grade 3 events, while 6 (1.6%) of the 386 TVE events were reported as Grade 4 or more events.

The Company performed a predefined meta-analysis of trial data to evaluate selected clinically important outcomes (mortality, TVE, and disease progression) for the cancer indication. The primary data set used in the meta-analysis included 3,104 patients from 12 completed, randomised, double-blinded, cancer trials for which patient-level data were available at the time of the analysis (2004). The overall HR from the primary meta-analysis for clinically relevant TVE occurrence for epoetin alfa compared with placebo was 1.44 (95% CI: 1.05, 1.98) consistent with previous experience in this population (ODAC 2007a, 2007b, 2007c).

When trials were grouped by intended HGB target, trials that targeted a HGB concentration beyond the correction of anaemia demonstrated a higher incidence of TVEs in both the control and epoetin alfa groups. Thromboembolic vascular events occurred in 96 (4.3%) of 2,228 patients in the control group and 188 (8.2%) of 2,292 patients in the epoetin alfa group. The HR was 1.98 (95% CI: 1.54, 2.55). For trials targeting HGB concentrations within the current labelled indication, TVEs occurred in 22 (1.8%) of 1,192 patients in the control group and 72 (4.2%) of 1,732 patients in the epoetin alfa group. The HR was 2.50 (95% CI: 1.54, 4.06).

Post-hoc, exploratory analyses of erythropoiesis-stimulating agent (ESA) treatment responders versus ESA treatment non-responders suggest that patients who fail to respond to epoetin alfa treatment after 4 or 8 weeks of therapy may have a higher risk for TVEs and adverse outcomes, although it cannot be determined from available data whether this risk is due to epoetin alfa treatment or inherent differences in the aggressiveness of the underlying malignancy that may have resulted in nonresponsiveness (ODAC 2007a, 2007b, 2007c).

Trial EPO-ANE-4008, a randomised, open-label, multicentre trial evaluating TVEs in patients with non-myeloid malignancies receiving chemotherapy and administered epoetin alfa once or 3 times a week for the treatment of anaemia, is completed. This trial demonstrated that in anaemic patients with non-myeloid malignancies receiving chemotherapy, when used within labelled guidance, the approved epoetin alfa dosing regimens of 450 IU/kg QW and 150 IU/kg 3 times per week (TIW) demonstrated comparable safety with respect to the incidence TVEs (2.1% for the QW group and 3.8% for the TIW group; difference, -1.8%, 95% CI: -5.1% to 1.6%, p=0.248) as determined by an independent adjudication committee through Week 16. The 2 regimens also demonstrated comparable efficacy with respect to HGB response and RBC transfusion utilisation.

Surgery

Thrombotic vascular events are a recognised risk in patients undergoing elective orthopaedic surgery (SmPC Section 4.4). In patients with a baseline HGB >13 g/dL, the possibility that epoetin alfa treatment may be associated with an increased risk of postoperative TVEs cannot be excluded. An analysis of adverse drug reactions (ADRs) conducted by the MAH across all indications in 2010 confirmed this (ADR Report 2010). This review of 408 patients requiring major, elective, orthopaedic surgery in 2 clinical studies demonstrated that the incidence of DVT was higher in the epoetin alfa group (16/261 [6%]) compared with the placebo-control group (6/147 [4%]); however, the customised group term “embolism and thrombosis” was comparable (19/261 [7%)] versus 10/147 [7%], in the epoetin alfa and placebo groups, respectively).

Among the 1,352 patients treated in surgery clinical trials with EPREX, there were 78 treatment-emergent TVEs. Of those 78 events, 47 (60%) were considered to be moderate to severe. Eighteen (23%) of the 78 TVE events were reported as serious adverse events.

Myelodysplastic Syndrome

Among the 102 patients treated in MDS clinical trials with EPREX, there were 2 treatment-emergent TVEs; one was Grade 1 severity and the other was Grade 3 severity. One of the 2 TVE events was reported as a serious adverse event. In addition to these 2 cases, there were 2 other cases, with reported terms of “sudden death” and “phlebitis” that were considered TVEs in Trial EPOANE3021. In the case of sudden death, stroke was considered as a possible cause of death by the investigator but was never confirmed. The event of phlebitis was distal DVT in nature.

Background Incidence/Prevalence:

Chronic Renal Failure

In a pooled analysis of 5 community-based cohorts from Europe and the United States, the pooled risk for overall VTE associated with CKD was 1.54 (95% CI: 1.15-2.06) when comparing individuals with CKD versus without CKD (Mahmoodi 2012a). The IR of VTE per 1,000 PY was estimated to be 1.5, 1.9, and 4.5 for patients with normal kidney function, mildly decreased renal function, and Stage 3 or 4 CKD, respectively, in a US study (Wattanaki 2008). A review summarised that the prevalence of renal vein thrombosis is up to 37% in patients with membranous glomerulonephritis, while DVT of the lower extremities can occur in up to 15% of patients with nephrotic syndrome (Singhal 2006).

Cancer

The overall risk of thrombosis in patients with cancer is 7-fold that of patients without cancer (Adess 2006). A review estimated the annual incidence of VTE to be 1 in 200 in a population of patients with cancer (Lee 2003).

Autologous Blood Donation

In a US study of postoperative thromboembolism in 2,043 patients who had a total hip arthroplasty, the incidence of DVT was significantly lower in those who donated blood preoperatively (9%) compared with those who had not (13.5%). Of those who donated blood, 0.3% developed postoperative pulmonary embolism compared with 0.7% in those who had not (Bae 2001). Similar conclusions about a lower incidence of DVT in those who donated blood preoperatively were also observed in a recent study in China (Lu 2013).

Surgery

A review of VTE in patients who underwent orthopaedic surgery indicated that without thromboprophylaxis, DVT may occur in up to 60% of patients within 2 weeks after lower extremity orthopaedic surgery (Kakkar 2013).

Myelodysplastic Syndrome

The majority of studies on thrombosis in MDS patients focus on specific drug exposures prior to the occurrence of thrombosis. One study, however, observed that among 5,673 MDS patients, 212 patients had an incident DVT (Smith 2012).

Risk Groups or Risk Factors:

Established VTE risk factors include surgery, cancer, hospitalisation, immobilisation, obesity, exogenous hormones, pregnancy and the puerperium, and inherited thrombophilia (Wattanakit 2009). Orthopaedic surgery, especially hip and knee joint replacement, multiple traumatisms, severe damage to the spine, or large fractures are risk factors for VTE. Patients

undergoing high-risk orthopaedic surgery who are not provided thromboprophylaxis have increased risk for VTE (Meza Reyes 2012).

Potential Mechanisms:

The risk of TVEs is primarily related to hypercoagulability, altered blood flow, and endothelial vascular lesions. Increased HCT is associated with increased blood viscosity, reduced venous return, and increased platelet adhesion. Patients with HCT levels above the normal range for the population are at an increased risk of TVEs. Relatively low plasma volume can also lead to increased blood viscosity and a higher risk of TVEs (Brækkan 2010). The literature suggests that epoetin alfa may transiently increase the number of circulating platelets and improve platelet function (Tang 1998).

Preventability:

For all patients: HGB should be closely monitored due to the potential increased risk of TVEs and fatal outcomes when patients are treated at HGB levels above the target for the indication of use.

The reported risk of TVEs should be carefully weighed against the benefits to be derived from treatment with EPREX, particularly in patients with pre-existing risk factors.

For CRF and cancer patients: Dose adjustments to maintain HGB values at the desired range between 10 to 12 g/dL.

For cancer patients: closely monitor patients to ensure that the lowest approved dose of ESA is used to provide adequate control of symptoms of anaemia.

For surgery patients: use of adequate antithrombotic prophylaxis during the perioperative period.

Impact on the Individual Patient:

Chronic Renal Failure

May lead to increased mortality and morbidity. Patients may need surgical interventions or procedures to treat thrombosis. Peripherally inserted central catheter lines may not be used for haemodialysis because of the increased risk of TVEs.

Cancer

May lead to increased mortality and morbidity. Patients may need surgical interventions or procedures to treat thrombosis (Bennett 2008).

Surgery

May lead to increased mortality and morbidity.

Potential Public Health Impact of Safety Concern:

May prolong hospitalisations and may require additional therapy to treat TVEs.

Evidence Source

Information regarding trials is provided in Annex 4.

Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report with data cutoff of 30 June 2015.

Adess 2006; ADR Report 2010; Bae 2001; Bennett 2008; Brækkan 2010; Kakkar 2013; Lee 2003; Lu 2013; Mahmoodi 2012a; Meza Reyes 2012; ODAC 2007a, 2007b, 2007c; Singhal 2006; Smith 2012; Tang 1998 Wattanakit 2008; Wattanakit 2009

MedDRA Terms:

Embolic and Thrombolic Events Standard MedDRA Query (SMQ)

Important Identified Risk – Pure Red Cell Aplasia

The risk of erythropoietin Ab-mediated PRCA was first identified in postauthorisation usage, beginning in 1998 and peaking in 2002. However, in the entire clinical trial database, there were only a total of 4 cases of PRCA reported in clinical trials, with 2 cases each reported for the oncology and MDS indications, respectively.

Oncology

Only 1 case of PRCA (Grade 2 severity) has been reported to date in patients with cancer who were receiving chemotherapy and treatment with EPREX in randomised clinical trials. The other case (Grade 1 severity) occurred in a non-ESA-treated patient. Neither case was considered a serious adverse event.

Myelodysplastic Syndrome

One case of PRCA was reported in each of the 2 clinical trials conducted in support of the MDS indication.

An event with an actual reported term of anti-erythropoietin Ab positive was reported in Trial EPOANE3021. The event was Grade 1 toxicity and reported in a subject in the epoetin alfa group that had anti-erythropoietin Abs (1:20, 1.0% cpm [a positive Ab was ≥0.9% cpm in the assay]) after Week 24. The event was considered related to the study agent and led to permanent discontinuation. There were no signs of PRCA reported in the bone marrow; serum erythropoietin remained detectable and reticulocytes were normal at the last available measurement. There were no subjects with documented PRCA during the study.

In Trial EPO-ANE-3018, there was 1 event of PRCA reported in the placebo group. The event was serious, Grade 3 toxicity, and considered by the investigator (while still blinded to treatment allocation) to be possibly related to the study agent.

Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Pure Red Cell Aplasia in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

	INDICATION: ONCOLOGY		
	Epoetin alfa (N=5827)	Non-ESA control (N=4719)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b]	5323	4719	
N			
Any Treatment-Emergent Event, n (%)	1 (0.02%)	1 (0.02%)	0.53 (0.03,8.20)
Outcome (Based on Serious AEs)	0	0	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	0 (0.00%)	
Recovered	0 (0.00%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Grade=1	0 (0.00%)	1 (0.02%)	
Grade=2	1 (0.02%)	0 (0.00%)	
Grade=3	0 (0.00%)	0 (0.00%)	
Grade>=4	0 (0.00%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	
Trials without control [c]	504	0	
N			
Any Treatment-Emergent Event, n (%)	0 (0.00%)	0 (0.00%)	N/A
Outcome (Based on Serious AEs)	0	0	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	0 (0.00%)	
Recovered	0 (0.00%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Grade=1	0 (0.00%)	0 (0.00%)	
Grade=2	0 (0.00%)	0 (0.00%)	
Grade=3	0 (0.00%)	0 (0.00%)	
Grade>=4	0 (0.00%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	
Combined (All Trials)	5827	4719	
N			
Any Treatment-Emergent Event, n (%)	1 (0.02%)	1 (0.02%)	
Outcome (Based on Serious AEs)	0	0	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	0 (0.00%)	
Recovered	0 (0.00%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Grade=1	0 (0.00%)	1 (0.02%)	
Grade=2	1 (0.02%)	0 (0.00%)	
Grade=3	0 (0.00%)	0 (0.00%)	
Grade>=4	0 (0.00%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	

Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Pure Red Cell Aplasia in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

INDICATION: ONCOLOGY

AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.

[b] Includes CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20 and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010

[c] Includes EPO-ANE-4008

Oncology Trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20 and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-ANE-4008, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010

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Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Pure Red Cell Aplasia in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

	INDICATION: MDS		
	Epoetin alfa (N=102)	Non-ESA control (N=53)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b]	102	53	
N			
Any Treatment-Emergent Event, n (%)	1 (0.98%)	1 (1.89%)	0.51 (0.03,7.70)
Outcome (Based on Serious AEs)	1	1	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	1 (0.98%)	1 (1.89%)	
Recovered	0 (0.00%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Grade=1	1 (0.98%)	0 (0.00%)	
Grade=2	0 (0.00%)	0 (0.00%)	
Grade=3	0 (0.00%)	1 (1.89%)	
Grade>=4	0 (0.00%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	
Combined (All Trials)	102	53	
N			
Any Treatment-Emergent Event, n (%)	1 (0.98%)	1 (1.89%)	
Outcome (Based on Serious AEs)	1	1	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	1 (0.98%)	1 (1.89%)	
Recovered	0 (0.00%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Grade=1	1 (0.98%)	0 (0.00%)	
Grade=2	0 (0.00%)	0 (0.00%)	
Grade=3	0 (0.00%)	1 (1.89%)	
Grade>=4	0 (0.00%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	

AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; MDS=myelodysplastic syndrome; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.
[b] Includes EPO-ANE-3018 and EPOANE3021

MDS Trials: EPO-ANE-3018 and EPOANE3021

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Postmarketing Experience:

Cumulatively, as of 30 June 2015, there have been 334 Ab-positive PRCA cases identified in patients with CRF. The majority (193 cases, 58%) involved exposure to EPREX in PS-80 uncoated stopper prefilled syringes (withdrawn from the market in 2004). Forty-one (37%) of the 111 cumulative cases of Ab-positive PRCA exposed to SC use of the currently marketed EPREX in PS-80 coated-stopper prefilled syringes only were reported from Thailand and 70 (63%) cases were reported outside of Thailand. The corresponding PRCA reporting rate in Thailand is unique to that country, is not EPREX-specific, and does not reflect the situation in the rest of the world. The Company's assessment of the worldwide reporting rate excluding Thailand in patients with CRF exposed to SC use of EPREX in PS-80 coated-stopper prefilled syringes (6.8 cases per 100,000 PY) more accurately reflects the baseline risk of Ab-positive PRCA associated with EPREX.

The Company has worked with the Thailand Health Authority and the Thailand Nephrology and Haematology Societies to identify possible reasons for the Thailand-specific reporting rate, including support of the Thai Registry, EPOANE4076. A total of 4,018 patients from 63 hospitals have been enroled in the Thai registry (EPOANE4076) since 2008. Enrolment was stopped by the primary investigator in June 2013. Of the 4,018 patients, approximately 400 patients (10%) received EPREX, while the remaining patients received non-EPREX brand ESA. Nine non-EPREX-brand ESA-related PRCA cases were reported, with an incidence of anti-r-HuEPO-associated PRCA case in Thailand of 1.7 cases per 1,000 PY exposure. The average exposure time was 13.6 months. No cases of Ab-mediated PRCA were identified with EPREX. Furthermore, the Company has an extensive worldwide pharmacovigilance monitoring programme for PRCA and has not detected any similar PRCA case clusters occurring at a single institution elsewhere in the world over the last 10 years.

Nature of Risk:

Pure red cell aplasia is a risk identified from postmarketing pharmacovigilance, not clinical trials. Cases of PRCA and reporting rates are proactively monitored and reported to health authorities periodically.

To date, only 2 cases of PRCA have been reported among EPREX-treated patients in clinical trials. Among the 5,827 patients treated in the cancer clinical trials with EPREX, there was 1 treatment-emergent event of PRCA in a patient with cancer who was receiving chemotherapy and treatment with EPREX. The other case was reported in a patient participating in a clinical trial for the MDS indication. Among the 102 patients treated in the MDS clinical trials with EPREX, there was 1 serious adverse event with an actual reported term of anti-erythropoietin positive (Grade 1 severity), for which PRCA was not confirmed.

The incidence of erythropoietin Ab-mediated PRCA associated with EPREX was elevated above the baseline rate associated with all ESAs for the period from 1998 to 2003 (RMP epoetin alfa 2005). The results of extensive quality, nonclinical, and clinical/epidemiologic investigations clearly support the conclusion that the transient increase in erythropoietin Ab-mediated PRCA between 1998 and 2003 was product-specific to EPREX and the increase over the background rate was associated with the use of 1 specific product presentation: the PS-80 EPREX formulation in prefilled syringes with uncoated rubber stoppers (1,000 IU to 4,000 IU and 10,000 IU strengths). The PS-80 EPREX vials and prefilled syringes in the 5,000 IU to 9,000 IU strengths have always been in coated-stopper presentations since their introduction in 1999 and 2000, respectively. Following the completion of a worldwide product recall in March 2004, the PS-80 EPREX formulation has been used exclusively in coated-stopper presentations. Since the introduction of this product presentation, the increased incidence associated with the PS-80 EPREX formulation in prefilled syringes with uncoated rubber stoppers has been resolved. The focus of this RMP is to describe the period of increased EPREX-specific PRCA, PRCA trends associated with the currently available PS-80 EPREX formulation in prefilled syringes with coated rubber stoppers, as well as ongoing pharmacovigilance and risk mitigation activities to ensure PRCA associated with the PS-80 EPREX formulation in prefilled syringes with coated rubber stoppers approximates the baseline risk associated with all ESAs.

An immunogenicity surveillance registry (Study EPO-ANE-4014) was conducted to provide assurance that the SC PS-80 EPREX formulation using coated stoppers had an acceptable immunogenic safety profile. The primary objective for this registry was to estimate the IR of erythropoietin Ab-mediated PRCA with SC exposure to the PS-80 formulation of EPREX and to compare this IR to that with SC exposure to other currently marketed recombinant erythropoietin products (epoetin beta [NeoRecormon®] and darbepoetin alfa [Aranesp®]) with adjustment for duration of exposure. Patients were to be observed for the development of PRCA for up to 3 years.

Study EPO-ANE-4014 enroled a total of 15,333 patients. There were 8,377 PY of exposure to EPREX and 14,286 PY of exposure to other ESAs. There were 3 cases of erythropoietin Ab-mediated PRCA with EPREX and 2 cases with other ESAs (1 case with Aranesp and 1 case with NeoRecormon) reported during the conduct of the registry. When comparing the IRs based on exposed time, the rate for the 3 EPREX cases was 35.8/100,000 PY, the rate for the 2 Aranesp/NeoRecormon cases combined was 14.0/100,000 PY, and the rate ratio was 2.6 (95% CI: 0.43, 15.31). The 90% and 95% CIs for the IRs overlap. Confidence intervals for the rate ratio overlap unity. The IR differences were not statistically significant (p-value was greater than 0.05).

Background Incidence/Prevalence:

The baseline erythropoietin Ab-mediated PRCA rate expected with all ESAs has not been quantified in interventional clinical trials. It is the Company's view that the PRCA reporting rates for EPREX cannot be directly compared with rates for other recombinant ESAs that are based upon spontaneous reports with different methods of case classification/adjudication, estimation, stimulation, selected time periods, and routes of administration.

Chronic Renal Failure

Recent findings from data collected on 15,333 patients with CKD, aged 18 years or older, enroled in the PRIMS observed 5 cases of confirmed Ab-mediated PRCA during the 3-year follow-up period. This translated to an IR of 35.8/100,000 PY for EPREX versus 14.0/100,000 PY (95% CI 1.7–50.6) for NeoRecormon®/Aranesp®. The incidence of erythropoietin Ab-mediated PRCA with EPREX was not significantly different versus comparator ESAs (rate ratio: 2.56; 95% CI 0.43–15.31). An analysis based on observed time produced similar findings.

The prevalence of pre-existing non-neutralising anti-ESA Abs in clinical trials of 1,235 nephrology patients was 5.75%, and the developing Ab rate in these patients was 2.43%. However, 101 of the 1,235 nephrology patients (8.2%) were determined to develop anti-ESA Ab after ESA treatment, although none of these patients demonstrated any signs of developing Ab-mediated PRCA. A small number of patients (1.7% in nephrology) had pre-existing Abs (baseline positive) that were post-dose Ab negative. Patients that had progressed to Ab-mediated PRCA were noted to have high Ab concentrations with neutralising activity and a diverse Immunoglobulin G (IgG) subtype (Barger 2012).

Cancer

According to a review on anti-erthropoietin Abs and PRCA, no cases of epoetin-induced PRCA had been reported in cancer patients on chemotherapy at the time of publication (Rossert 2004).

Surgery

The incidence and prevalence data on PRCA and patients undergoing orthopaedic surgery are not detailed in the literature.

Myelodysplastic Syndrome

Myelodysplastic syndrome with PRCA was identified in a total of 16 (2.9%) patients among 550 consecutive adult MDS patients diagnosed in a US hospital (Wang 2007).

***Risk Groups or Risk Factors*:**

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 (Macdougall 2005). 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 (Macdougall 2012).

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.

Potential Mechanisms:

Development of Abs to erythropoietin causes an isolated disorder of erythropoiesis that leads to a severe, isolated anaemia with sudden onset. Epoetin alfa is a recombinant version of a human protein, and therefore, the mechanism is likely related to autoimmunity and disrupting B-cell tolerance. The mechanisms by which tolerance is disrupted are not entirely understood. The presence of aggregates may be a key factor in triggering activation of autoreactive B cells: the periodicity of self-antigens present in protein aggregates is similar to the repeated self-epitope structure of viral capsids that can directly activate B cells (Schellekens 2006, Van Beers 2010, Macdougall 2012).

The timing of the increase in the rate of PRCA in 1998 was consistent with the introduction of the EPREX PS-80 formulation and is consistent with the formulation switch. Further investigations demonstrated that this formulation was associated with the appearance of leachates in EPREX prefilled syringes that used an uncoated rubber stopper. These leachates have been demonstrated in mouse studies to enhance the immune response to foreign protein in a dose-dependent fashion (Ryan 2006).

The results of extensive quality, nonclinical, and clinical/epidemiologic investigations clearly support the conclusion that the transient increase in PRCA between 1998 and 2003 was product-specific to EPREX, and the increase over the background rate was associated with the use of 1 specific product presentation: the PS-80 EPREX formulation in prefilled syringes with uncoated rubber stoppers (1,000 IU-4,000 IU and 10,000 IU strengths) (Boven 2005).

Anaemia from PRCA can be managed with blood transfusion and is reversible for many patients with immunosuppressive treatments (Casadevall 2005; Eckardt 2003).

Preventability:

Since the PS-80 EPREX formulation has been available exclusively in coated-stopper presentations, the IR of erythropoietin Ab-mediated PRCA associated with SC EPREX use in patients with CKD has dropped and now approximates the background/baseline level.

Immunogenicity to any therapeutic protein is potentially increased by product degradation and aggregation. To minimise the risk of this, the Company maintains and monitors an appropriate continuous cold chain for storage and handling of EPREX from point of manufacture to the final distribution agent.

In patients with CRF where IV access is routinely available (haemodialysis patients), administration by the IV route is preferable. Such IV use will further reduce the baseline risk, because the IV route is generally associated with the lowest risk of immunogenicity for therapeutic proteins.

Patients with CRF treated with epoetin alfa by the SC route should be monitored regularly for loss of efficacy, defined as absent or decreased response to epoetin alfa treatment in patients who previously responded to such therapy. This is characterised by a sustained decrease in HGB despite an increase in epoetin alfa dosage. In patients developing sudden lack of efficacy defined by a decrease in HGB (1 to 2 g/dL per month) with increased need for transfusions, a reticulocyte count should be obtained and typical causes of non-response (eg, iron, folate, or Vitamin B12 deficiency, aluminium intoxication, infection or inflammation, blood loss, and haemolysis and bone marrow fibrosis of any origin) should be investigated.

A paradoxical decrease in HGB and development of severe anaemia associated with low reticulocyte counts should prompt to discontinue treatment with EPREX and perform anti-erythropoietin Ab testing. A bone marrow examination should also be considered for diagnosis of PRCA.

No other ESA therapy should be commenced because of the risk of cross reaction.

Antibody-mediated PRCA has been reported after months to years of mostly SC epoetin treatment mainly in patients with CRF. Very rarely, cases have been reported with IV epoetin use as well. Cases have also been reported in patients with hepatitis C treated with interferon and ribavirin, when ESAs are used concomitantly. EPREX is not approved for the management of anaemia associated with hepatitis C.

Impact on the Individual Patient:

Patients may develop severe erythropoietin-resistant anaemia that may require repeated transfusions. Patients may develop PRCA, which needs to be treated with immunosuppressive/immunomodulatory therapies such as cyclosporine or prednisone. Alternatives to ESA treatment include RBC transfusions, which have inherent risks.

Potential Public Health Impact of Safety Concern:

At the peak incidence, EPREX product-specific PRCA was a rare event (>1/10,000, <1/1,000 PY), with a cumulative reporting rate of 46.9/100,000 PY. The cumulative reporting rate of Ab-positive PRCA for EPREX is 17.3 cases per 100,000 PYs for SC use (10.5 cases per 100,000 PY excluding Thailand) and 0.2 cases per 100,000 PYs for IV use. Anaemia from PRCA can be managed by blood transfusions and is reversible for many patients with immunosuppressive treatment alone or with immunosuppressive treatment associated with renal transplantation (Eckardt, 2003; Bennett 2005). After Ab levels have decreased, patients can be treated again with IV EPREX. The public health impact is, therefore, considered low.

Evidence Source:

Study EPO-ANE-4014 (PRIMS), Annex 4.

Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report with data cutoff of 30 June 2015.

Semiannual Immunogenicity Report, August 2015.

Barger 2012; Bennett 2005; Boven 2005; Casadevall 2005, Eckardt 2003; Macdougall 2005; Macdougall 2012; RMP epoetin alfa 2005; Rossert 2004; Ryan 2006; Schellekens 2006; Van Beers 2010; Wang 2007

MedDRA Terms:

The following preferred terms were used for PRCA: anti-erythropoietin Ab, anti-erythropoietin Ab positive, Ab test abnormal, Ab test positive, aplasia pure red cell, drug-specific Ab present, inhibiting Abs, neutralising Abs.

Important Identified Risk – Hypertension/Hypertensive Crisis

Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Hypertension in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

INDICATION: CHRONIC RENAL FAILURE - DIALYSIS			
	Epoetin alfa (N=2046)	Non-ESA control (N=46)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b]	97	46	
N			
Any Treatment-Emergent Event, n (%)	5 (5.15%)	0 (0.00%)	N/A
Outcome (Based on Serious AEs)	0	0	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	0 (0.00%)	
Recovered	0 (0.00%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Mild	2 (2.06%)	0 (0.00%)	
Moderate	2 (2.06%)	0 (0.00%)	
Severe	1 (1.03%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	
Trials without control [c]	1949	0	
N			
Any Treatment-Emergent Event, n (%)	340 (17.4%)	0 (0.00%)	N/A
Outcome (Based on Serious AEs)	29	0	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	3 (0.15%)	0 (0.00%)	
Recovered	26 (1.33%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Mild	177 (9.08%)	0 (0.00%)	
Moderate	121 (6.21%)	0 (0.00%)	
Severe	42 (2.15%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	
Combined (All Trials)	2046	46	
N			
Any Treatment-Emergent Event, n (%)	345 (16.9%)	0 (0.00%)	
Outcome (Based on Serious AEs)	29	0	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	3 (0.15%)	0 (0.00%)	
Recovered	26 (1.27%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Mild	179 (8.75%)	0 (0.00%)	
Moderate	123 (6.01%)	0 (0.00%)	
Severe	43 (2.10%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	

AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.

[b] Includes EP86-001 (CEO-C01), EP86-004

[c] Includes EPO-CAN-1, EPO-CAN-13, EPO-INT-37, EPO-INT-68, EPO-INT-77, EPO-ITA-2, ZEO-107 (CCP107P108), ZEO-121 (CC2574P121), ZEO-S01 (CCP102P103)

Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004, EPO-CAN-1, EPO-CAN-13, EPO-INT-37, EPO-INT-68, EPO-INT-77, EPO-ITA-2, ZEO-107 (CCP107P108), ZEO-121 (CC2574P121), ZEO-S01 (CCP102P103)

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Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Hypertension in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

INDICATION: CHRONIC RENAL FAILURE - PREDIALYSIS			
	Epoetin alfa (N=5610)	Non-ESA control (N=325)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b]	464	325	
N			
Any Treatment-Emergent Event, n (%)	86 (18.5%)	66 (20.3%)	1.08 (0.74,1.58)
Outcome (Based on Serious AEs)	2	1	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	1 (0.22%)	1 (0.31%)	
Recovered	1 (0.22%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Mild	33 (7.11%)	26 (8.00%)	
Moderate	48 (10.3%)	37 (11.4%)	
Severe	5 (1.08%)	3 (0.92%)	
Unknown	0 (0.00%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	
Trials without control [c]	5146	0	
N			
Any Treatment-Emergent Event, n (%)	602 (11.7%)	0 (0.00%)	N/A
Outcome (Based on Serious AEs)	58	0	
Fatal	1 (0.02%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	2 (0.04%)	0 (0.00%)	
Recovered	44 (0.86%)	0 (0.00%)	
N/A	11 (0.21%)	0 (0.00%)	
Severity, n (%)			
Mild	271 (5.27%)	0 (0.00%)	
Moderate	273 (5.31%)	0 (0.00%)	
Severe	55 (1.07%)	0 (0.00%)	
Unknown	3 (0.06%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	
Combined (All Trials)	5610	325	
N			
Any Treatment-Emergent Event, n (%)	688 (12.3%)	66 (20.3%)	
Outcome (Based on Serious AEs)	60	1	
Fatal	1 (0.02%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	3 (0.05%)	1 (0.31%)	
Recovered	45 (0.80%)	0 (0.00%)	
N/A	11 (0.20%)	0 (0.00%)	
Severity, n (%)			
Mild	304 (5.42%)	26 (8.00%)	
Moderate	321 (5.72%)	37 (11.4%)	
Severe	60 (1.07%)	3 (0.92%)	
Unknown	3 (0.05%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	

AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.

[b] Includes EPO-AUS-14, EPO-CAN-10, EPO-ITA-7, EPOCKD2002, G86-011, H87-054

[c] Includes CHOIR (PR00-06014), EPOCKD2001, EPO-AKD-3001, EPO-AKD-3002, EPO-INT-14, G86-053, G86-125, H87-055, N93-063, POWER (PR00-06009), PROMPT (PR01-06021), Q2W INITIATION (PR03-06001), EPO-NED-15

Chronic Renal Failure – Predialysis Trials: CHOIR (PR00-06014), EPOCKD2001, EPOCKD2002, EPO-AKD-3001, EPO-AKD-3002, EPO-AUS-14, EPO-CAN-10, EPO-INT-14, EPO-ITA-7, G86-011, G86-053, G86-125, H87-054, H87-055, N93-063, POWER (PR00-06009), PROMPT (PR01-06021), Q2W INITIATION (PR03-06001), EPO-NED-15

Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Hypertension in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

	INDICATION: ONCOLOGY		
	Epoetin alfa (N=5827)	Non-ESA control (N=4719)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b]	5323	4719	
N			
Any Treatment-Emergent Event, n (%)	148 (2.78%)	119 (2.52%)	1.11 (0.87,1.43)
Outcome (Based on Serious AEs)	5	5	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	1 (0.02%)	0 (0.00%)	
Recovered	3 (0.06%)	3 (0.06%)	
N/A	1 (0.02%)	2 (0.04%)	
Severity, n (%)			
Grade=1	68 (1.28%)	54 (1.14%)	
Grade=2	57 (1.07%)	50 (1.06%)	
Grade=3	21 (0.39%)	15 (0.32%)	
Grade>=4	0 (0.00%)	0 (0.00%)	
Unknown	2 (0.04%)	0 (0.00%)	
Trials without control [c]	504	0	
N			
Any Treatment-Emergent Event, n (%)	9 (1.79%)	0 (0.00%)	N/A
Outcome (Based on Serious AEs)	0	0	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	0 (0.00%)	
Recovered	0 (0.00%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Grade=1	6 (1.19%)	0 (0.00%)	
Grade=2	3 (0.60%)	0 (0.00%)	
Grade=3	0 (0.00%)	0 (0.00%)	
Grade>=4	0 (0.00%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	
Combined (All Trials)	5827	4719	
N			
Any Treatment-Emergent Event, n (%)	157 (2.69%)	119 (2.52%)	
Outcome (Based on Serious AEs)	5	5	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	1 (0.02%)	0 (0.00%)	
Recovered	3 (0.05%)	3 (0.06%)	
N/A	1 (0.02%)	2 (0.04%)	
Severity, n (%)			
Grade=1	74 (1.27%)	54 (1.14%)	
Grade=2	60 (1.03%)	50 (1.06%)	
Grade=3	21 (0.36%)	15 (0.32%)	
Grade>=4	0 (0.00%)	0 (0.00%)	
Unknown	2 (0.03%)	0 (0.00%)	

Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Hypertension in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

INDICATION: ONCOLOGY

AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.

[b] Includes CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20 and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010

[c] Includes EPO-ANE-4008

Oncology Trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20 and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-ANE-4008, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010

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Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Hypertension in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

INDICATION:AUTOLOGOUS BLOOD DONATION

	Epoetin alfa (N=402)	Non-ESA control (N=242)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b] N	402	242	
Any Treatment-Emergent Event, n (%)	6 (1.49%)	5 (2.07%)	0.72 (0.21,2.48)
Outcome (Based on Serious AEs)	N/A	N/A	
Severity, n (%)			
Mild	1 (0.25%)	1 (0.41%)	
Moderate	0 (0.00%)	2 (0.83%)	
Severe	0 (0.00%)	0 (0.00%)	
Missing	5 (1.24%)	2 (0.83%)	
Combined (All Trials) N	402	242	
Any Treatment-Emergent Event, n (%)	6 (1.49%)	5 (2.07%)	
Outcome (Based on Serious AEs)	N/A	N/A	
Severity, n (%)			
Mild	1 (0.25%)	1 (0.41%)	
Moderate	0 (0.00%)	2 (0.83%)	
Severe	0 (0.00%)	0 (0.00%)	
Missing	5 (1.24%)	2 (0.83%)	

ABD=autologous blood donation; AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.

[b] Includes CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058

ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058.

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Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Hypertension in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

	INDICATION:SURGERY		
	Epoetin alfa (N=1352)	Non-ESA control (N=922)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b]	1207	922	
N			
Any Treatment-Emergent Event, n (%)	108 (8.95%)	52 (5.64%)	1.26 (0.88,1.81)
Outcome (Based on Serious AEs)	0	1	
Fatal	0 (0.00%)	1 (0.11%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	0 (0.00%)	
Recovered	0 (0.00%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Mild	55 (4.56%)	24 (2.60%)	
Moderate	41 (3.40%)	21 (2.28%)	
Severe	12 (0.99%)	7 (0.76%)	
Unknown	0 (0.00%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	
Trials without control [c]	145	0	
N			
Any Treatment-Emergent Event, n (%)	11 (7.59%)	0 (0.00%)	N/A
Outcome (Based on Serious AEs)	0	0	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	0 (0.00%)	
Recovered	0 (0.00%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Mild	4 (2.76%)	0 (0.00%)	
Moderate	7 (4.83%)	0 (0.00%)	
Severe	0 (0.00%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	
Combined (All Trials)	1352	922	
N			
Any Treatment-Emergent Event, n (%)	119 (8.80%)	52 (5.64%)	
Outcome (Based on Serious AEs)	0	1	
Fatal	0 (0.00%)	1 (0.11%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	0 (0.00%)	
Recovered	0 (0.00%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Mild	59 (4.36%)	24 (2.60%)	
Moderate	48 (3.55%)	21 (2.28%)	
Severe	12 (0.89%)	7 (0.76%)	
Unknown	0 (0.00%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	

AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.

[b] Includes EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, PR97-19-002 (spine)

[c] Includes N93-057

Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, N93-057, PR97 19 002 (spine)

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Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Hypertension in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

	INDICATION: MDS		
	Epoetin alfa (N=102)	Non-ESA control (N=53)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b]	102	53	
N			
Any Treatment-Emergent Event, n (%)	6 (5.88%)	3 (5.66%)	1.05 (0.25,4.38)
Outcome (Based on Serious AEs)	0	0	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	0 (0.00%)	
Recovered	0 (0.00%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Grade=1	3 (2.94%)	1 (1.89%)	
Grade=2	1 (0.98%)	1 (1.89%)	
Grade=3	2 (1.96%)	1 (1.89%)	
Grade>=4	0 (0.00%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	
Combined (All Trials)	102	53	
N			
Any Treatment-Emergent Event, n (%)	6 (5.88%)	3 (5.66%)	
Outcome (Based on Serious AEs)	0	0	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	0 (0.00%)	
Recovered	0 (0.00%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Grade=1	3 (2.94%)	1 (1.89%)	
Grade=2	1 (0.98%)	1 (1.89%)	
Grade=3	2 (1.96%)	1 (1.89%)	
Grade>=4	0 (0.00%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	

AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; MDS=myelodysplastic syndrome; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.
[b] Includes EPO-ANE-3018 and EPOANE3021

MDS Trials: EPO-ANE-3018 and EPOANE3021

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Postmarketing Experience:

The cumulative reporting rate for hypertension (which may include hypertensive crisis or other related terms) in the postmarketing setting is 4.3 cases per 100,000 PY based on 4,575,083 PY of cumulative exposure through 30 June 2015.

Nature of Risk:

Chronic Renal Failure

A history of hypertension is a risk factor for CHF in patients on dialysis. Among the 2,046 adult patients treated in adult haemodialysis trials with EPREX, there were 345 treatment-emergent hypertension events. Of those 345 hypertension events, 166 (48%) were considered to be moderate to severe. Twenty-nine (<1%) of the 345 hypertension events were reported as serious adverse events. Among the 5,610 adult patients treated in adult predialysis clinical trials with EPREX, there were 688 treatment-emergent hypertension events. Of those 688 hypertension events, 381 (55%) were considered to be moderate to severe. Sixty (<1%) of the 688 hypertension events were reported as serious adverse events.

Cancer

Among the 5,827 adult patients treated in cancer clinical trials with EPREX, there were 157 treatment-emergent hypertension events. Of those 157 events, 60 (38%) were Grade 2 and 21 (13%) were Grade 3. Five (3%) of the 157 hypertension events were reported as serious adverse events.

Autologous Blood Donation

Of the 402 patients treated in the ABD clinical trials with epoetin alfa, there were only 6 (1.49%) treatment-emergent hypertension events reported. One of the events was mild in severity, while severity was missing for the other 5 events.

Surgery

Among the 1,352 adult patients treated in orthopaedic surgery clinical trials with EPREX, there were 119 treatment-emergent hypertension events. Of those 119 events, 60 (50%) were considered to be moderate to severe. There were no reports of hypertension as serious adverse events in EPREX-treated surgical patients. Antiplatelet therapy may prevent the development of hypertension in patients treated with epoetin alfa (Caravaca 1994).

Myelodysplastic Syndrome

Among the 102 adult patients treated in the MDS clinical trials with EPREX, there were 6 treatment-emergent hypertension events. Of those 6 events, 3 events were Grade 1, 1 event was Grade 2, and 2 events were Grade 3. None of the hypertension events were reported as serious adverse events.

Background Incidence/Prevalence:

Chronic Renal Failure

Arterial hypertension develops in up to 80% of renal transplant recipients (Basić-Jukić 2007). In a large nationally representative sample of adults in England, hypertension was prevalent in 25.4% of patients with CKD (Kearns 2013). Hypertension prevalence by CKD stage is provided in a US national survey of non-institutionalised adults, which estimates that hypertension occurs in 35.8% of Stage 1, 48.1% of Stage 2, 59.9% of Stage 3, and 84.1% of Stage 4 to 5 patients with

CKD (USRDS 2010). Hypertension is found in more than 50% of paediatric patients with CKD, although its prevalence varies according to the cause of CKD (Van DeVoorde 2011). In a large nationally representative sample of adults in England, hypertension was prevalent in 4.5% of patients with mildly impaired eGFR, 63.9% of those with Stage 3 to 5 CKD, and 79.3% of those with Stage 5 CKD (Jameson 2014).

Cancer

Among patients with cancer, hypertension has been observed to be the most common comorbidity with a prevalence of 37% (Piccirillo 2004). However, the prevalence of 29% prior to chemotherapy was found to be similar to the general population (Maitland 2010). A restrospective cohort study was conducted to estimate IRs of new-onset hypertension in adult cancer patients identified from the Varian Medical Oncology outpatient database in the United States. New-onset hypertension was observed in about one-third of 25,090 patients with various types of cancer. The IRs of severe and crisis-level hypertension, respectively, were the highest in patients with gastric (18.5 cases per 100 PY, 5.6 per 100 PY) and ovarian cancer (20.2 per 100 PY, 4.8 per 100 PY). The highest IR of moderate hypertension was observed in patients with renal cancer (46.7 per 100 PY). Across all cancers, chemotherapy exposure was associated with a 2- to 3.5-fold increase in risk of any degree of hypertension compared with periods of no chemotherapy; higher hypertension levels demonstrated greater variability in RRs by type and line of therapy but indicated an overall increase associated with chemotherapy exposure (Fraeman 2013).

Surgery

According to US NHDS data, the prevalence of hypertension among patients undergoing total arthroplasty from 1990 to 2004 was 37.54% (Liu 2009). Another study that included patients in the United Kingdom reported that 49.3% of TKR patients also had hypertension (Oleske 2014).

Myelodysplastic Syndrome

In a US study of 600 MDS patients, approximately 55% of patients were diagnosed with a disorder of the cardiovascular system, with hypertension being the most common comorbidity at 27% (Naqvi 2011). A small retrospective chart review of 26 patients who had received a diagnosis of both chronic myeloid disorders and pulmonary hypertension observed that 2 patients had MDS (Dingli 2001). Another study of 88 MDS patients observed hypertension to be present in 45.4% of patients (De Roos 2010).

Risk Factors:

Risk factors for hypertension include increasing age, African-American race, family history of hypertension, being overweight or obese, physical inactivity, tobacco use, dietary factors (excess sodium, insufficient potassium, and vitamin D), stress, and alcohol (Mayo Clinic, high blood pressure 2012).

Potential Mechanisms:

Postulated mechanisms for epoetin alfa-induced hypertension include increased viscosity or vasoconstrictive responses due to the correction of anaemia (Kanbay 2007). Experiments designed to study the vascular sequelae (hypertension and thrombosis) of epoetin alfa treatment have revealed that endothelial cells have large numbers of epoetin alfa receptors and that epoetin alfa enhances their proliferation and migration in vitro (Lappin 2007).

Preventability:

In all patients receiving epoetin alfa, blood pressure should be closely monitored and controlled as necessary. Epoetin alfa should be used with caution in the presence of untreated, inadequately treated, or poorly controllable hypertension. It may be necessary to add or increase antihypertensive treatment. If blood pressure cannot be controlled, epoetin alfa treatment should be discontinued.

Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have occurred also during epoetin alfa treatment in patients with previously normal or low blood pressure. Particular attention should be paid to sudden stabbing migraine-like headaches as a possible warning signal.

In patients with CRF, the rate of increase in HGB should not exceed 2 g/dL (1.25 mmol/l) per month to minimise risks of hypertension. Maintenance HGB concentrations should not exceed the upper limit of the HGB concentration range as recommended in Section 4.2 of the SmPC (12 g/dL [7.5 mmol/L]). In clinical trials, an increased risk of death and serious cardiovascular events was observed when ESAs were administered to achieve a HGB concentration greater than 12 g/dL. In patients with CRF and cancer, HGB concentrations should be monitored regularly until a stable level is achieved, and periodically thereafter.

Impact on the Individual Patient:

There is a potential for increased morbidity and mortality.

Potential Public Health Impact of Safety Concern:

Chronic renal failure is a global public health concern, and there is emerging a strong relationship between CRF and increased CVD risk. Chronic renal failure in the presence of other comorbidities such as hypertension and Type 2 diabetes mellitus can lead to early progression to ESRD (Stage V CRF) and confer a greater risk for CVD morbidity and mortality than is seen among patients with CRF who do not have these comorbidities (Yerram 2007).

In general, hypertension is very prevalent in the patient population being treated with EPREX, therefore, the additional public health impact associated with this safety risk is considered low.

Evidence Source:

Information regarding trials is provided in Annex 4.

Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report with data cutoff of 30 June 2015.

SmPC

Basić-Jukić 2007; Caravaca 1994; DeRoos 2010; Dingli 2001; Fraeman 2013; Jameson 2014; Kanbay 2007; Kearns 2013; Lappin 2007; Liu 2009; Maitland 2010; Mayo Clinic 2012, high blood pressure; Naqvi 2011; Oleske 2014; Piccirillo 2004; USRDS 2010; Van DeVoorde 2011; Yerram 2007

MedDRA Terms:

Hypertension SMQ; scope=narrow

Important Potential Risks

Important Potential Risk – Disease Progression

Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Disease Progression in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

	INDICATION: ONCOLOGY		
	Epoetin alfa (N=5827)	Non-ESA control (N=4719)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b] N	5323	4719	
Any Treatment-Emergent Event, n (%)	292 (5.49%)	249 (5.28%)	1.00 (0.81,1.23)
Outcome (Based on Serious AEs)	74	48	
Fatal	11 (0.21%)	5 (0.11%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	29 (0.54%)	17 (0.36%)	
Recovered	18 (0.34%)	15 (0.32%)	
N/A	16 (0.30%)	11 (0.23%)	
Severity, n (%)			
Grade=1	7 (0.13%)	6 (0.13%)	
Grade=2	34 (0.64%)	27 (0.57%)	
Grade=3	117 (2.20%)	79 (1.67%)	
Grade>=4	0 (0.00%)	1 (0.02%)	
Unknown	134 (2.52%)	136 (2.88%)	
Trials without control [c] N	504	0	
Any Treatment-Emergent Event, n (%)	61 (12.1%)	0 (0.00%)	N/A
Outcome (Based on Serious AEs)	41	0	
Fatal	29 (5.75%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	10 (1.98%)	0 (0.00%)	
Recovered	1 (0.20%)	0 (0.00%)	
N/A	1 (0.20%)	0 (0.00%)	
Severity, n (%)			
Grade=1	5 (0.99%)	0 (0.00%)	
Grade=2	8 (1.59%)	0 (0.00%)	
Grade=3	32 (6.35%)	0 (0.00%)	
Grade>=4	15 (2.98%)	0 (0.00%)	
Unknown	1 (0.20%)	0 (0.00%)	
Combined (All Trials) N	5827	4719	
Any Treatment-Emergent Event, n (%)	353 (6.06%)	249 (5.28%)	
Outcome (Based on Serious AEs)	115	48	
Fatal	40 (0.69%)	5 (0.11%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	39 (0.67%)	17 (0.36%)	
Recovered	19 (0.33%)	15 (0.32%)	
N/A	17 (0.29%)	11 (0.23%)	
Severity, n (%)			
Grade=1	12 (0.21%)	6 (0.13%)	
Grade=2	42 (0.72%)	27 (0.57%)	
Grade=3	149 (2.56%)	79 (1.67%)	
Grade>=4	15 (0.26%)	1 (0.02%)	
Unknown	135 (2.32%)	136 (2.88%)	

Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Disease Progression in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.

[b] Includes CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20 and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010

[c] Includes EPO-ANE-4008

Oncology Trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20 and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-ANE-4008, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010

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Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Disease Progression in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

INDICATION: MDS			
	Epoetin alfa (N=102)	Non-ESA control (N=53)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b] N	102	53	
Any Treatment-Emergent Event, n (%)	4 (3.92%)	1 (1.89%)	2.17 (0.24,20.0)
Outcome (Based on Serious AEs)	4	1	
Fatal	1 (0.98%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	3 (2.94%)	1 (1.89%)	
Recovered	0 (0.00%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Grade=1	0 (0.00%)	0 (0.00%)	
Grade=2	2 (1.96%)	0 (0.00%)	
Grade=3	1 (0.98%)	1 (1.89%)	
Grade>=4	1 (0.98%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	
Combined (All Trials) N	102	53	
Any Treatment-Emergent Event, n (%)	4 (3.92%)	1 (1.89%)	
Outcome (Based on Serious AEs)	4	1	
Fatal	1 (0.98%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	3 (2.94%)	1 (1.89%)	
Recovered	0 (0.00%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Grade=1	0 (0.00%)	0 (0.00%)	
Grade=2	2 (1.96%)	0 (0.00%)	
Grade=3	1 (0.98%)	1 (1.89%)	
Grade>=4	1 (0.98%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	

AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; MDS=myelodysplastic syndrome; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.
[b] Includes EPO-ANE-3018 and EPOANE3021
MDS Trials: EPO-ANE-3018 and EPOANE3021

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Postmarketing Experience

As of 30 June 2015, a cumulative search of the postmarketing database identified 35 cases of disease progression in patients with cancer. Of these cases, 21 cases reported a fatal outcome. The cumulative reporting rate of disease progression for the cancer indication in the postmarketing setting is 0.8 cases per 100,000 PY, based on 4,575,083 PYs of cumulative exposure through 30 June 2015.

Nature of Risk:

Cancer

This important potential risk only involves patients treated for CIA.

None of the Company's supportive-care trials has rigorously assessed tumour outcomes utilising methods that would be appropriate to the development of cancer therapeutic agents. In general, trials have lacked the necessary tumour and treatment homogeneity for this assessment because they were designed to evaluate haematologic endpoints, not tumour outcome, as the primary efficacy measure. Response-based endpoints are difficult to interpret because of the requirement that patients enter the trial only after becoming anaemic during chemotherapy administration rather than entering at the commencement of chemotherapy. Therefore, PFS from the time of first epoetin alfa administration, as measured in these supportive-care trials, is actually quite different from PFS normally reported in trials of therapeutic cancer agents (where it is measured from the onset of chemotherapy treatment).

Tumour progression as the basis for excess mortality observed in some clinical trials remains an unresolved issue. Although theoretically plausible, it has not been consistently supported by preclinical data or in clinical trials, notwithstanding methodologic limitations inherent to supportive-care cancer trials. Plausible alternatives (eg, TVEs at high HGB targets) need also to be considered as a potential cause of excess mortality seen in a few trials.

Comprehensive analyses of patient-level data from controlled clinical trials with epoetin alfa, when used in the setting of CIA, demonstrate a neutral effect on overall survival and tumour progression while demonstrating clear benefit in terms of reducing the need for blood transfusion (ODAC 2007a, 2007b, 2007c).

The Company is evaluating the impact of epoetin alfa on tumour outcome including PFS and survival in an appropriately designed clinical trial (Trial EPO-ANE-3010).

Among the 5,827 adult patients treated in cancer trials with EPREX, there were 353 treatment-emergent disease-progression events. Of those 353 events, 149 (42%) were Grade 3 and 15 (4%) were Grade ≥4. One hundred and fifteen of the 353 disease-progression events were reported as serious adverse events.

Myelodysplastic Syndrome

Among the 102 adult patients treated in MDS clinical trials with EPREX, there were 4 treatment emergent disease-progression events. Of those 4 events, 2 (50%) were Grade 2 severity, 1 (25%) was Grade 3 severity, and 1 (25%) was Grade 4 severity. All of the disease-progression events were reported as serious adverse events.

In the Phase 3 MDS trial (EPOANE3021), the individual treatment-emergent adverse event terms used by the investigator to report diseases were different from the pooled-analysis terms used in above clinical trial data. Based on actual visit dates, 6 (7.1%) patients in the epoetin alfa group and 4 (8.9%) patients in the placebo group had disease progression reported during the

first 24 weeks of the study. Individual treatment-emergent adverse events used by the investigators to report disease progression were coded as MDS (2 patients in the epoetin group), acute myelogenous leukaemia (AML, 1 patient in the epoetin alfa group, 2 patients in the placebo group), refractory anaemia with excess blasts (1 patient in each group), leukaemia (1 patient in the epoetin alfa group), thrombocytopaenia (1 patient in the epoetin alfa group), and disease progression (1 patient in the placebo group). During the entire trial period, 14 (16.5%) patients in the epoetin alfa group and 4 (8.9%) patients in the placebo group had disease progression. No patients in the placebo group had disease progression after the first 24 weeks. However, only 1 of 45 patients in placebo group entered into the extension phase and had follow up after Week 28. Based on actual visit dates, an additional 8 (9.4%) patients in the epoetin alfa group had disease progression reported after the first 24 weeks of the trial. Individual treatment-emergent adverse events used by the investigators to report disease progression after the first 24 weeks were coded as MDS (3 patients), AML (1 patient), and disease progression (4 patients).

Overall, among the subjects who experienced disease progression, there were 5 who progressed to AML (3 [3.5%] in the epoetin alfa group and 2 [4.4%] in the placebo group); all progressions to AML occurred prior or at Week 24.

Background Incidence/Prevalence:

Chronic Renal Failure

The risk of disease progression is associated with the cancer indication only.

Cancer

Progression of cancer can vary by cancer type. For example, according to a review of ductal carcinoma in situ cases, results from large clinical trials and follow-up trials suggest that, if left untreated, up to 50% of ductal carcinoma in situ lesions progress to invasive disease, and time for progression may be up to 4 decades (Saunders 2005; Collins 2005; Jones 2006). In non-muscle invasive bladder cancer, progression can occur in ≤45% of patients at stage pT1 and carcinoma in situ (van Rhijn 2009).

Surgery

The risk of disease progression is associated with the cancer indication only.

Myelodysplastic Syndrome

In a retrospective analysis of 856 patients with low- or intermediate-1-risk MDS, only 10% of patients in this series transformed to AML (Garcia-Manero, 2010), while a review noted that the risk of progression to AML is 25% to 35% at 5 years. Specifically, the median time to 25% AML evolution is 9.4 years for low risk, 2.5 years for intermediate risk, 1.7 years for high risk, and 0.7 years for very high-risk MDS disease (Fenaux 2014).

Risk Factors:

Risk factors of disease progression depend on the type of cancer. Disease progression in oncology patients can depend on environmental and psychological factors.

Potential Mechanisms:

Preclinical in vitro and in vivo data do not provide convincing evidence that erythropoietin promotes tumour growth and proliferation. Although there is no convincing evidence from clinical trials that epoetin alfa promotes tumour growth, theoretical mechanisms include: 1) direct tumour promotion through an interaction with epoetin receptors expressed on the surface of tumour cells, 2) promotion of tumour vascularisation leading to promotion of tumour growth.

Preventability:

The perceived increased risk of disease progression or death with epoetin alfa treatment was observed in settings where either epoetin alfa was administered to achieve HGB levels beyond the correction of anaemia (>12 g/dL), or in the setting of cancer-induced anaemia in patients not receiving concomitant anticancer treatment and in the setting of patients with head and neck cancer receiving radiotherapy only.

Impact on the Individual Patient:

Decreased survival in patients with cancer.

Potential Public Health Impact of Safety Concern:

Decreased PFS time in patients with cancer.

Evidence Source:

Information regarding cancer trials is provided in Annex 4.

Collins 2005; Fenaux 2014; Garcia-Manero 2010; Jones 2006; ODAC 2007a, 2007b, 2007c; Saunders 2005; van Rhijn 2009.

MedDRA Terms:

The following preferred terms were used for disease progression: condition aggravated, disease progression, malignant neoplasm progression, neoplasm progression

Important Potential Risk – Survival Impact

Survival data were not collected as an endpoint in surgery clinical trials. Therefore a frequency table for this potential risk is not provided for the surgery indication.

Survival or mortality data were collected in some of the cancer and CRF clinical 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. In addition, a mortality safety signal was only observed in cancer or CRF clinical trials that were conducted outside of the approved indications or the current treatment guidelines. Given these reasons, simple frequency tables without considering the above important variability can be misleading, and hence are not provided. Instead, findings related to this potential risk in cancer and CRF clinical trials are each described in the corresponding sections below.

No data from previous cancer and CRF clinical trials indicated decreased survival due to the administration of EPREX according to the approved indications and treatment guidelines.

The Company is evaluating the impact of epoetin alfa on tumour outcome including PFS and survival in an appropriately designed clinical trial (Trial EPO-ANE-3010). Trial EPO-ANE-3010 is a randomised, open-label, multicentre, Phase 3 international trial of epoetin alfa plus best standard supportive care versus standard supportive care alone in anaemic patients with metastatic breast cancer receiving standard chemotherapy. The trial was conducted in 2,098 anaemic women with metastatic breast cancer, who received first- or second-line chemotherapy. This was a noninferiority trial designed to rule out a 15% risk increase in tumour progression or death of epoetin alfa plus standard-of-care as compared with standard-of-care alone. The trial will end once approximately 1,650 patients have died.

As of the clinical cutoff date of 07 July 2014 for the CSR, the median PFS per investigator assessment of disease progression was 7.4 months in each arm (HR 1.09, 95% CI: 0.99, 1.20), indicating the study objective was not met. Median PFS with disease progression assessed by the Independent Review Committee was 7.6 months in each arm (HR 1.03, 95% CI: 0.92, 1.15). At clinical cutoff, 1,337 deaths were reported. Median overall survival in the epoetin alfa plus standard-of-care group was 17.2 months compared with 17.4 months in the standard-of-care alone group (HR 1.06, 95% CI: 0.95, 1.18).

Myelodysplastic Syndrome

In the Phase 3 MDS trial (EPOANE3021), 4 (4.7%) patients in the epoetin alfa group and 1 (2.2%) patient in the placebo group had at least 1 treatment-emergent adverse event with onset during the first 24 weeks, which resulted in death during or after the first 24 weeks. One subject in each group died due to AML and the other 3 deaths in the epoetin alfa group were due to sudden death, cachexia, and renal failure.

There were 3 more deaths in the epoetin alfa group that were due treatment-emergent adverse events with onset after the first 24 weeks of the study: 1 death occurred during the 4-week follow-up period after Week 24, congestive cardiac failure; and 2 deaths occurred due to a treatment-emergent adverse event with onset during the treatment extension phase: sudden death and disease progression. However, only 1 out of 45 patients in the placebo arm entered into extension phase and had follow up after Week 28

The deaths due cachexia, CHF, and disease progression in the epoetin alfa group and AML in the placebo group all occurred more than 30 days after the last dose of the study drug.

None of the deaths was considered by the investigators to be related to the study drug.

Postmarketing Experience:

Survival in patients mainly depends on the underlying tumour type, and frequency in the postmarketing environment is difficult to calculate as limited information is available. Therefore, the exact frequency for this risk cannot be provided.

Nature of Risk:

Chronic Renal Failure

The Company has performed comprehensive meta-analyses to evaluate selected clinically important outcomes, including mortality, in epoetin alfa trials in CKD (dialysis or predialysis).

The Company thoroughly examined the relationship between ESA dose requirements, the achieved HGB response versus the target HGB level, and clinical outcomes in patients with CKD (Cardiovascular and Renal Drugs Advisory Committee [CRDAC] 2007). These results suggest that, while the high HGB-target group demonstrated a higher risk for the primary composite event endpoint, the risk is predominantly observed for the patients within this group who exhibited poor ESA response. A similar but somewhat weaker relationship between poor response and increased risk was also observed in the low HGB-target group.

In a combined analysis of 8 published studies conducted in non-dialysis CKD and 4 published studies in haemodialysis (CRDAC 2007), the RR for mortality for the higher-HGB target groups versus the lower-HGB target groups is not significant. For non-dialysis CKD, the RR is 1.01 (95% CI: 0.63, 1.61), and in haemodialysis, the RR is 1.12 (95% CI: 0.91, 1.37).

A meta-analysis reported by Phrommintikul et al included a total of 9 studies: 4 in haemodialysis and 5 in non-dialysis CKD. The primary finding was a significantly higher risk of all-cause mortality (risk ratio 1.17 [95% CI: 1.01, 1.35]; p=0.031) in the higher-HGB target group than in the lower-HGB target group in the fixed-effects model without heterogeneity between studies (Phrommintikul 2007).

A meta-analysis of the risks of cardiovascular morbidity in patients with CKD treated with ESAs was conducted (CHMP Response 2014). The following is a brief summary of the Company's investigation of epoetin alfa. Data from 27 Company-sponsored trials were pooled to evaluate

efficacy or safety of epoetin alfa treatment in adults with CKD. A total of 7,254 patients who received at least 1 dose of epoetin alfa in the 27 trials were included in the analyses. Twenty of the 27 trials enroled patients who were not receiving dialysis (N=5,624), and the remaining 7 trials enroled patients who were receiving dialysis (N=1,630). There were 11 correction trials (designed to correct anaemia with ESA treatment), 8 maintenance trials (designed to maintain relatively stable levels of HGB with ESA treatment), and 8 other trials. The 27 trials, which were conducted over a period of 20 years, were never intended to be pooled for analysis. Trial designs, patient populations, duration of treatment, target HGB concentrations, and other key features varied considerably from trial to trial. The trials ranged in duration from 8 weeks to up to 3 years. The entry criteria and target levels of HGB varied between trials, with target HGB levels as high as 14 g/dL in a few trials. The protocol-specified epoetin alfa dose regimens also varied; some trials had weight-based initial doses while others had fixed initial doses.

The analyses investigating the association between mean achieved HGB (continuous) in the 3-month period prior to an event and the outcomes of interest provided very consistent results suggesting that higher achieved HGB is associated with a decreased risk of occurrence of all-cause mortality. The HR for all-cause mortality was 0.721 (95% CI: 0.643, 0.807) for all patients in the combined studies. This result suggests that, for each 1 g/dL increase in mean achieved HGB over the 3-month window, the risk of death from any cause decreased by approximately 28% (1 minus 0.721). The HRs for patients receiving dialysis, patients not receiving dialysis, patients in the correction studies, and patients in the maintenance studies were similar to that for all patients.

The analyses investigating the association between cumulative epoetin alfa dose in the 3-month period prior to an event and the outcomes of interest provided results that, taken as a whole, suggest an association between higher cumulative epoetin alfa doses and an increased risk of deaths due to any cause. The HRs of the second-, third-, and fourth- dose quartiles of cumulative epoetin alfa dose (>3,214 to ≤6,250 IU/wk, >6,250 to ≤10,583 IU/wk, and >10,583 IU/wk) versus the first quartile (reference category, ≤3,214 IU/wk) were greater than 1 for all-cause mortality.

Based on the information from the analyses above, the Company concludes that the HGB concentration in patients should be targeted at between 10 and 12 g/dL, as concentrations above this range may be associated with increased mortality.

Cancer

A meta-analysis conducted by Amgen, Inc. and the Company of 59 controlled clinical trials (epoetin alfa and darbepoetin alfa) in CIA has reported data for on-trial deaths or deaths during long-term follow up (ODAC 2008). Of these 59 trials, a meta-analysis of the data from the 19 trials that reported long-term survival data (≥1 year of follow up) demonstrated an overall neutral survival risk associated with ESA use, with an OR (ESA versus control) of 1.00 (95% CI: 0.89, 1.12). Data from 8 of the 59 trials have suggested a potential negative effect of epoetin alfa on survival in patients with cancer. All 8 trials were conducted in treatment settings not approved for epoetin alfa.

The safety signals observed in the trials in question are inconsistent in that some trials reported potential negative effects during the treatment period (as early as 4 months in Trial EPO-INT-76), while others reported differences in mortality only after many years of follow up (Trials 20000161, GOG-191, and a Phase 3 trial of Aranesp in neoadjuvant breast cancer [PREPARE]).

Overall, these signals have not been consistently observed in individual trials, and meta-analyses in over 8,000 patients do not indicate a clear effect of epoetin alfa on mortality in the CIA population. Other controlled trials of ESAs also performed outside of the labelled indication, but considered to be informative with respect to mortality and/or tumour progression, have not suggested an increased risk of these events.

If, after 8 weeks, the HGB 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 (SmPC Section 4.2).

It is the Company's position that the data presented by the Company and Amgen Inc. during the 2007 and 2008 meetings of the US Food and Drug Administration (FDA) Oncology Drugs Advisory Committee (ODAC 2007a, 2007b, 2007c; ODAC 2008) demonstrated no adverse effect on mortality and survival in patients with cancer receiving chemotherapy and treatment with ESAs according to product labelling guidelines.

Surgery

Epoetin alfa has been studied in placebo-controlled, double-blind trials of patients scheduled for major, elective, orthopaedic surgery. Although an increased incidence of DVT in patients receiving epoetin alfa undergoing surgical orthopaedic procedures has been observed, there is no evidence of excess mortality observed for the epoetin alfa treatment group.

In a randomised, placebo-controlled trial of epoetin alfa in adults who were undergoing coronary artery bypass surgery (Annex 4, Trial H87-083), 7 of 126 patients in the epoetin alfa group died whereas no deaths were reported among the 56 patients in the placebo group. Four of the deaths occurred during the period of trial drug administration, and all 4 deaths were associated with TVEs. Perisurgical use of epoetin alfa in patients with severe coronary artery disease is not recommended and is contraindicated in the SmPC (SmPC Section 4.3).

Background Incidence/Prevalence:

Not applicable.

Risk Factors:

Cardiovascular deaths account for about 40% of all deaths of patients with CRF, particularly those on dialysis (Couser 2011).

There is some evidence to suggest that lifestyle factors such as obesity and physical inactivity after cancer diagnosis could contribute to poorer disease outcomes (Wei 2010). Among patients who have undergone hip surgery, risk factors for early mortality most commonly identified are increasing age, male gender, and comorbid conditions, especially CVD (Berstock, 2014).

Potential Mechanisms:

Although the mechanism by which epoetin alfa may affect survival of patients with cancer is not completely understood, concern exists over the potential for epoetin alfa to directly affect tumour outcome. It is known that TVEs are under-diagnosed as a proximate cause of death in patients with cancer. Thus, it is plausible that TVEs could represent a mechanism for increased mortality associated with epoetin alfa in patients with cancer.

Exploratory analyses of response to epoetin alfa treatment suggest that patients with cancer failing to achieve a 1 g/dL rise in HGB by 4 or 8 weeks of treatment have higher morbidity and mortality, although it cannot be determined whether this is due to epoetin alfa treatment or to inherent differences in the underlying malignancy.

Preventability:

When used according to labelled guidance for correction of anaemia in the setting of CIA (as well as CRF), there is no evidence that epoetin alfa has an adverse effect on survival. However, the data strongly suggest that epoetin alfa treatment increases the risk for death and serious cardiovascular events when administered to a target HGB concentration >12 g/dL. Patients should be monitored closely to ensure that the lowest approved dose of ESA is used to provide adequate control of symptoms of anaemia.

Impact on the Individual Patient:

Potential increased risk of death.

Potential Public Health Impact of Safety Concern:

May lead to increased mortality.

Evidence Source:

Information regarding cancer trials is provided in Annex 4.

Berstock 2014; CHMP Response 2014; Couser 2011; CRDAC 2007; ODAC 2007a, 2007b, 2007c; ODAC 2008; Phrommintikul 2007; Wei 2010

MedDRA Terms:

Survival impact was not collected in clinical trials and therefore there are no preferred terms.

Important Potential Risk – Congestive Heart Failure

Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Congestive Heart Failure in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

INDICATION: CHRONIC RENAL FAILURE - DIALYSIS			
	Epoetin alfa (N=2046)	Non-ESA control (N=46)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b]	97	46	
N			
Any Treatment-Emergent Event, n (%)	1 (1.03%)	1 (2.17%)	0.51 (0.03,8.32)
Outcome (Based on Serious AEs)	0	0	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	0 (0.00%)	
Recovered	0 (0.00%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Mild	1 (1.03%)	0 (0.00%)	
Moderate	0 (0.00%)	1 (2.17%)	
Severe	0 (0.00%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	
Trials without control [c]	1949	0	
N			
Any Treatment-Emergent Event, n (%)	146 (7.49%)	0 (0.00%)	N/A
Outcome (Based on Serious AEs)	40	0	
Fatal	1 (0.05%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	6 (0.31%)	0 (0.00%)	
Recovered	33 (1.69%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Mild	67 (3.44%)	0 (0.00%)	
Moderate	46 (2.36%)	0 (0.00%)	
Severe	33 (1.69%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	
Combined (All Trials)	2046	46	
N			
Any Treatment-Emergent Event, n (%)	147 (7.18%)	1 (2.17%)	
Outcome (Based on Serious AEs)	40	0	
Fatal	1 (0.05%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	6 (0.29%)	0 (0.00%)	
Recovered	33 (1.61%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Mild	68 (3.32%)	0 (0.00%)	
Moderate	46 (2.25%)	1 (2.17%)	
Severe	33 (1.61%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	

AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.

[b] Includes EP86-001 (CEO-C01), EP86-00

[c] Includes EPO-CAN-1, EPO-CAN-13, EPO-INT-37, EPO-INT-68, EPO-INT-77, EPO-ITA-2, ZEO-107 (CCP107P108), ZEO-121 (CC2574P121), ZEO-S01 (CCP102P103)

Chronic Renal Failure – Dialysis Trials: EP86-001 (CEO-C01), EP86-004, EPO-CAN-1, EPO-CAN-13, EPO-INT-37, EPO-INT-68, EPO-INT-77, EPO-ITA-2, ZEO-107 (CCP107P108), ZEO-121 (CC2574P121), ZEO-S01 (CCP102P103)

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Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Congestive Heart Failure in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

INDICATION: CHRONIC RENAL FAILURE - DIALYSIS			
	Epoetin alfa (N=5610)	Non-ESA control (N=325)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b]	464	325	
N			
Any Treatment-Emergent Event, n (%)	80 (17.2%)	66 (20.3%)	0.91 (0.62,1.33)
Outcome (Based on Serious AEs)	8	6	
Fatal	2 (0.43%)	1 (0.31%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	1 (0.22%)	1 (0.31%)	
Recovered	5 (1.08%)	4 (1.23%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Mild	38 (8.19%)	35 (10.8%)	
Moderate	32 (6.90%)	22 (6.77%)	
Severe	9 (1.94%)	9 (2.77%)	
Unknown	1 (0.22%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	
Trials without control [c]	5146	0	
N			
Any Treatment-Emergent Event, n (%)	777 (15.1%)	0 (0.00%)	N/A
Outcome (Based on Serious AEs)	253	0	
Fatal	18 (0.35%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	6 (0.12%)	0 (0.00%)	
Recovered	188 (3.65%)	0 (0.00%)	
N/A	41 (0.80%)	0 (0.00%)	
Severity, n (%)			
Mild	321 (6.24%)	0 (0.00%)	
Moderate	297 (5.77%)	0 (0.00%)	
Severe	148 (2.88%)	0 (0.00%)	
Unknown	11 (0.21%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	
Combined (All Trials)	5610	325	
N			
Any Treatment-Emergent Event, n (%)	857 (15.3%)	66 (20.3%)	
Outcome (Based on Serious AEs)	261	6	
Fatal	20 (0.36%)	1 (0.31%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	7 (0.12%)	1 (0.31%)	
Recovered	193 (3.44%)	4 (1.23%)	
N/A	41 (0.73%)	0 (0.00%)	
Severity, n (%)			
Mild	359 (6.40%)	35 (10.8%)	
Moderate	329 (5.86%)	22 (6.77%)	
Severe	157 (2.80%)	9 (2.77%)	
Unknown	12 (0.21%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	

AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.

[b] Includes EPO-AUS-14, EPO-CAN-10, EPO-ITA-7, EPOCKD2002, G86-011, H87-054

[c] Includes CHOIR (PR00-06014), EPOCKD2001, EPO-AKD-3001, EPO-AKD-3002, EPO-INT-14, G86-053, G86-125, H87-055, N93-063, POWER (PR00-06009), PROMPT (PR01-06021), Q2W INITIATION (PR03-06001), EPO-NED-15

Chronic Renal Failure – Predialysis Trials: CHOIR (PR00-06014), EPOCKD2001, EPOCKD2002, EPO-AKD-3001, EPO-AKD-3002, EPO-AUS-14, EPO-CAN-10, EPO-INT-14, EPO-ITA-7, G86-011, G86-053, G86-125, H87-054, H87-055, N93-063, POWER (PR00-06009), PROMPT (PR01-06021), Q2W INITIATION (PR03-06001), EPO-NED-15

Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Congestive Heart Failure in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

	INDICATION: ONCOLOGY		
	Epoetin alfa (N=5827)	Non-ESA control (N=4719)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b]	5323	4719	
N			
Any Treatment-Emergent Event, n (%)	420 (7.89%)	336 (7.12%)	1.13 (0.97,1.32)
Outcome (Based on Serious AEs)	28	24	
Fatal	3 (0.06%)	4 (0.08%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	8 (0.15%)	4 (0.08%)	
Recovered	16 (0.30%)	15 (0.32%)	
N/A	1 (0.02%)	1 (0.02%)	
Severity, n (%)			
Grade=1	219 (4.11%)	181 (3.84%)	
Grade=2	146 (2.74%)	105 (2.23%)	
Grade=3	49 (0.92%)	40 (0.85%)	
Grade>=4	2 (0.04%)	3 (0.06%)	
Unknown	4 (0.08%)	7 (0.15%)	
Trials without control [c]	504	0	
N			
Any Treatment-Emergent Event, n (%)	23 (4.56%)	0 (0.00%)	N/A
Outcome (Based on Serious AEs)	5	0	
Fatal	4 (0.79%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	0 (0.00%)	
Recovered	1 (0.20%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Grade=1	14 (2.78%)	0 (0.00%)	
Grade=2	2 (0.40%)	0 (0.00%)	
Grade=3	3 (0.60%)	0 (0.00%)	
Grade>=4	3 (0.60%)	0 (0.00%)	
Unknown	1 (0.20%)	0 (0.00%)	
Combined (All Trials)	5827	4719	
N			
Any Treatment-Emergent Event, n (%)	443 (7.60%)	336 (7.12%)	
Outcome (Based on Serious AEs)	33	24	
Fatal	7 (0.12%)	4 (0.08%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	8 (0.14%)	4 (0.08%)	
Recovered	17 (0.29%)	15 (0.32%)	
N/A	1 (0.02%)	1 (0.02%)	
Severity, n (%)			
Grade=1	233 (4.00%)	181 (3.84%)	
Grade=2	148 (2.54%)	105 (2.23%)	
Grade=3	52 (0.89%)	40 (0.85%)	
Grade>=4	5 (0.09%)	3 (0.06%)	
Unknown	5 (0.09%)	7 (0.15%)	

AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.

[b] Includes CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20 and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-CAN 15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010

[c] Includes EPO-ANE-4008

Oncology Trials: CISPLATIN (I88-036, OEO-U24 and OEO-U25), NON-CHEMOTHERAPY (H87-032, OEO-U20 and OEOU21), NON-CISPLATIN (I88-037, OEO-U22 and OEO-U23), AGO/NOGGO (EPO-GER-8), EP92-002, EPO-ANE-4008, EPO-CAN-15, EPO-CAN-17, EPO-CAN-20, EPO-CAN-203, EPO-CAN-303, EPO-GBR-4, EPO-GBR-7, EPO-GER-20, EPO-GER-22, EPO-GOG-191, EPO-INT-1 (2574-P-416), EPO-INT-10 (EPO-C111-457), EPO-INT-2 (CC2574-P-467), EPO-INT-3 (2574-P-034), EPO-INT-45, EPO-INT-47, EPO-INT-49, EPO-INT-50, EPO-INT-51 (EPO-CA-484), EPO-INT-76 (EPO-CA-489), EPO-J89-040 (J89-040), EPO-N93-004 (N93-004), EPO-P-169 (2574-P-169), EPO-P-174 (CC2574-P-174), MOEBUS, OBE/EPO-INT-03, PR00-03-006, PR00-27-005, PR98-27-008, PR99-11-034/044, PRI/EPO-NED-17, RTOG/PR99-03-046 (PR99-03-046), EPO-CAN-29, EPO-ANE-3010

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Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Congestive Heart Failure in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

INDICATION: AUTOLOGOUS BLOOD DONATION			
	Epoetin alfa (N=402)	Non-ESA control (N=242)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b] N	402	242	
Any Treatment-Emergent Event, n (%)	6 (1.49%)	7 (2.89%)	0.39 (0.12,1.30)
Outcome (Based on Serious AEs)	N/A	N/A	
Severity, n (%)			
Mild	5 (1.24%)	5 (2.07%)	
Moderate	1 (0.25%)	1 (0.41%)	
Severe	0 (0.00%)	1 (0.41%)	
Missing	0 (0.00%)	0 (0.00%)	
Combined (All Trials) N	402	242	
Any Treatment-Emergent Event, n (%)	6 (1.49%)	7 (2.89%)	
Outcome (Based on Serious AEs)	N/A	N/A	
Severity, n (%)			
Mild	5 (1.24%)	5 (2.07%)	
Moderate	1 (0.25%)	1 (0.41%)	
Severe	0 (0.00%)	1 (0.41%)	
Missing	0 (0.00%)	0 (0.00%)	

ABD=autologous blood donation; AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.

[b] Includes CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058

ABD Trials: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058

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Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Congestive Heart Failure in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

	INDICATION:SURGERY		
	Epoetin alfa (N=1352)	Non-ESA control (N=922)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b]	1207	922	
N			
Any Treatment-Emergent Event, n (%)	92 (7.62%)	48 (5.21%)	1.14 (0.77,1.69)
Outcome (Based on Serious AEs)	0	2	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	1 (0.11%)	
Recovered	0 (0.00%)	1 (0.11%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Mild	59 (4.89%)	28 (3.04%)	
Moderate	26 (2.15%)	16 (1.74%)	
Severe	7 (0.58%)	4 (0.43%)	
Unknown	0 (0.00%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	
Trials without control [c]	145	0	
N			
Any Treatment-Emergent Event, n (%)	10 (6.90%)	0 (0.00%)	N/A
Outcome (Based on Serious AEs)	0	0	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	0 (0.00%)	
Recovered	0 (0.00%)	0 (0.00%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Mild	7 (4.83%)	0 (0.00%)	
Moderate	2 (1.38%)	0 (0.00%)	
Severe	1 (0.69%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	
Combined (All Trials)	1352	922	
N			
Any Treatment-Emergent Event, n (%)	102 (7.54%)	48 (5.21%)	
Outcome (Based on Serious AEs)	0	2	
Fatal	0 (0.00%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	1 (0.11%)	
Recovered	0 (0.00%)	1 (0.11%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Mild	66 (4.88%)	28 (3.04%)	
Moderate	28 (2.07%)	16 (1.74%)	
Severe	8 (0.59%)	4 (0.43%)	
Unknown	0 (0.00%)	0 (0.00%)	
Missing	0 (0.00%)	0 (0.00%)	

AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.
[b] Includes EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, PR97-19-002 (spine)
[c] Includes N93-057

Surgery Trials: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, N93-057, PR97-19-002 (spine)

Frequency (Odds Ratio, 95% Confidence Interval), SAE Outcomes, and Severity of Congestive Heart Failure in Randomised Controlled Clinical Trials, Clinical Trials Without Control, and All Clinical Trials

	INDICATION: MDS		
	Epoetin alfa (N=102)	Non-ESA control (N=53)	Odds Ratio [a] (95% CI)
Randomised Controlled Trials [b] N	102	53	
Any Treatment-Emergent Event, n (%)	7 (6.86%)	6 (11.3%)	0.58 (0.19,1.81)
Outcome (Based on Serious AEs)	2	1	
Fatal	1 (0.98%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	0 (0.00%)	
Recovered	1 (0.98%)	1 (1.89%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Grade=1	3 (2.94%)	4 (7.55%)	
Grade=2	2 (1.96%)	2 (3.77%)	
Grade=3	2 (1.96%)	0 (0.00%)	
Grade>=4	0 (0.00%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	
Combined (All Trials) N	102	53	
Any Treatment-Emergent Event, n (%)	7 (6.86%)	6 (11.3%)	
Outcome (Based on Serious AEs)	2	1	
Fatal	1 (0.98%)	0 (0.00%)	
Hospitalised	0 (0.00%)	0 (0.00%)	
Not Recovered	0 (0.00%)	0 (0.00%)	
Recovered	1 (0.98%)	1 (1.89%)	
N/A	0 (0.00%)	0 (0.00%)	
Severity, n (%)			
Grade=1	3 (2.94%)	4 (7.55%)	
Grade=2	2 (1.96%)	2 (3.77%)	
Grade=3	2 (1.96%)	0 (0.00%)	
Grade>=4	0 (0.00%)	0 (0.00%)	
Unknown	0 (0.00%)	0 (0.00%)	

AE=adverse event; CI=confidence interval; ESA=erythropoiesis-stimulating agent; MDS=myelodysplastic syndrome; N/n=number; N/A=not applicable

[a] The stratified Mantel-Haenszel odds ratio (stratified by trial) was used.

[b] Includes: EPO-ANE-3018 and EPOANE3021

MDS Trials: EPO-ANE-3018 and EPOANE3021

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Postmarketing Experience:

The cumulative reporting rate for CHF in the postmarketing setting is 1.9 cases per 100,000 PY based on 4,575,083 PY of cumulative EPREX exposure through 30 June 2015.

Nature of Risk:

Chronic Renal Failure

Among the 2,046 patients treated in adult haemodialysis trials with EPREX, there were 147 treatment-emergent CHF events. Of those 147 events, 79 (54%) were considered to be moderate to severe. Forty (27%) of the 147 CHF events were reported as serious adverse events.

Among the 5,610 patients treated in adult predialysis trials with EPREX, there were 857 treatment-emergent CHF events. Of those 857 events, 486 (57%) were considered to be moderate to severe. Two hundred sixty-one (30%) of the 857 CHF events were reported as serious adverse events.

The Company has performed comprehensive meta-analyses to evaluate CHF in epoetin alfa trials in CKD (dialysis or predialysis).

For Analysis Set I (16 trials in which patients were treated with epoetin alfa, regardless of HGB target), the CHF rate for predialysis patients treated with epoetin alfa was 4.5% (95% CI: 2.9, 6.7%). In patients receiving dialysis (n=712), the corresponding rate was 2.9% (95% CI: 1.8, 4.6%). For Analysis Set II (meta-analyses of event rates by target HGB [10 to 12 g/dL or >12 g/dL] from all 19 trials), the CHF rates in predialysis patients treated with epoetin alfa were 5.7% (95% CI: 3.6, 8.7%) and 3.8% (95% CI: 1.9, 7.7%) in the 10 to 12 g/dL and >12 g/dL groups, respectively. In patients receiving dialysis, the corresponding rates were 3.0% (95% CI: 1.8, 4.9%) and 2.3% (95% CI: 0.6, 8.7%) in the 10 to 12 g/dL and >12 g/dL groups, respectively. For Analysis Set III (meta-analyses of event rates by target HGB [10 to 12 g/dL or >12 g/dL] from 6 trials randomised by high- and low-HGB targets), the OR in predialysis patients treated with epoetin alfa was 1.45 (95% CI: 1.05, 2.01) for the >12-g/dL group versus the 10- to 12-g/dL group. No formal statistical analysis was conducted for patients receiving dialysis as there was only 1 event in the >12 g/dL group and no events in the 10- to 12-g/dL group.

The MAH conducted a more recent meta-analysis of the safety of epoetins on patients with CKD (CHMP Response 2014). The analyses investigating the association between mean achieved HGB (continuous) in the 3-month period prior to an event provided very consistent results suggesting that higher achieved HGB is associated with a decreased risk of occurrence of cardiovascular events (a composite of events that included heart failure). The HR for cardiovascular events was 0.854 (95% CI: 0.763, 0.955) for all patients in the combined trials. This result suggests that, for each 1 g/dL increase in mean achieved HGB over the 3-month window, the risk of cardiovascular events decreased by approximately 15%. The HRs for patients receiving dialysis, patients not receiving dialysis, patients in the correction trials, and patients in the maintenance trials were similar to that for all patients.

The analyses investigating the association between cumulative epoetin alfa dose in the 3-month period prior to an event provided results that, taken as a whole, suggest an association between higher cumulative epoetin alfa doses and an increased risk of deaths due to cardiovascular events (a composite of events that included heart failure). However, causality cannot be ascertained, the

associations were not uniformly consistent in all analyses, and there was no clear dose-dependent increase. The HRs of the second-, third-, and fourth-- dose quartiles of cumulative epoetin alfa dose (>3,214 to ≤6,250 IU/wk, >6,250 to ≤10,583 IU/wk, and >10,583 IU/wk) versus the first quartile (reference category, ≤3,214 IU/wk) were greater than 1 for cardiovascular events.

Cancer

Among the 5,827 adult patients treated in cancer trials with EPREX, there were 443 treatment-emergent CHF events. Of those 443 events, 148 (33%) were considered to be Grade 2 and 52 (12%) were considered to be Grade 3. Thirty-three (7%) of the 443 CHF events were reported as serious adverse events.

Autologous Blood Donation

Among the 402 adult patients treated in orthopaedic surgery clinical trials with EPREX, there were 6 treatment-emergent CHF events. Of those 6 events, 1 (16.7%) was considered to be moderate or severe. There were no reports of CHF as serious adverse events in EPREX-treated ABD patients.

Surgery

Among the 1,352 adult patients treated in orthopaedic surgery clinical trials with EPREX, there were 102 treatment-emergent CHF events. Of those 102 events, 36 (35%) were considered to be moderate to severe. There were no reports of CHF as serious adverse events in EPREX-treated surgical patients.

Myelodysplastic Syndrome

Among the 102 adult patients treated in the MDS clinical trials with EPREX, there were 7 treatment-emergent CHF events. Of those 7 events, 3 events were Grade 1, 2 events were Grade 2, and 2 events were Grade 3. Two (29%) of the CHF events were reported as serious adverse events.

Background Incidence/Prevalence:

Chronic Renal Failure

According to 1 review, the prevalence of heart failure is about 37% among patients upon starting dialysis (Lisowska 2004). Another review (Schiffrin 2007) summarised the cardiovascular risk by CKD stage. Specifically, risk estimates of cardiovascular risk were 1.5 for CKD Stage 2, ranged from 2 to 4 for Stage 3, ranged from 4 to 10 for Stage 4, and ranged from 10 to 50 for Stage 5. The younger the person, higher the RR compared with people who did not have CKD.

Cancer

A nationwide study in Sweden observed a 70% greater overall incidence of coronary heart disease in patients with cancer compared with the general population without cancer. The IR was highest for leukaemia and cancers of the small intestine, kidney, lung, and liver during the first 6 months of diagnosis (Zöller 2012). Reviews have also reported on incidence of different types of cardiovascular morbidity (such as CHF) in relation to specific antineoplastic drugs

(Senkus 2011; Khakoo 2008). Prevalence of comorbid CVD has been reported separately for specific cancer types in different studies. For instance, according to a US Medicare study of patients with breast cancer aged 66 years and older, the prevalence of CVD at the time of cancer diagnosis was 12.8% (Patnaik 2011). In a hospital-based study in Italy, of the 189 patients who underwent surgery for non-small cell lung cancer, 17.5% had concurrent CVD (Pavia 2007). A high prevalence of cardiovascular comorbidity of 52% has been observed among patients with metastatic colorectal cancer (Overbeek 2012). In another study of 5,077 patients with prostate cancer in the United States, 256 patients had CHF or MI at baseline (Nanda 2009).

Surgery

In a US population-based study of patients with hip fractures, the prevalence of preoperative heart failure was 27% and rates of postoperative heart failure were 6.7% at 7 days and 21.3% at 1 year (Cullen 2011). Results from a US nationwide inpatient survey of cases of elective bilateral knee arthroplasty found the complications-weighted prevalence of CHF to be 11.8% (Memtsoudis 2011).

Myelodysplastic Syndrome

A cohort of 840 MDS patients in an Italian study reported that cardiac disease was the most frequently observed (25%) comorbidity. The frequency of CHF or ejection fraction <50% was 19% (Della Porta, 2011). In a US study of 52 elderly MDS patients, the prevalence of CHF was 48.2% (Goldberg, 2010).

Risk Factors:

Known risk factors for CHF are hypertension, diabetes, coronary artery disease, heart attack, certain diabetes medications, certain anticancer treatments and chemotherapy medications, radiation therapy applied to the heart area, sleep apnoea, congenital heart defects, viruses, alcohol use, and irregular heartbeats (Mayo Clinic, 2015: heart failure; Mayo Clinic, 2015: cancer).

Potential Mechanisms:

In CHF, an increase in HGB concentration is associated with a reduction in ejection fraction and an increase in blood pressure.

Inflammation and associated oxidative stress interact with erythropoiesis at several levels. Pro-inflammatory cytokines and inflammatory mediators suppress native erythropoietin production and blunt response to erythropoietin at the receptor level. Patients with CKD with the combination of wasting and inflammation are most likely to have more severe anaemia and to be hyporesponsive to epoetin alfa. Congestive heart failure is associated with elevated levels of pro-inflammatory cytokines, which may contribute to wasting and anaemia (Bárány 2007).

Preventability:

The recommended desired HGB concentration range is between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/l). EPREX should be administered in order to increase HGB to not greater than

12 g/dL (7.5 mmol/l). A rise in HGB of greater than 2 g/dL (1.25 mmol/l) over a 4-week period or a sustained HGB level of greater than 12 g/dL (7.5 mmol/l) should be avoided.

Haemoglobin concentrations should be monitored closely to ensure that the lowest approved dose of EPREX is used to provide adequate control of anaemia while maximising the patients' safety.

Impact on the Individual Patient:

Potential for increased morbidity and mortality.

Potential Public Health Impact of Safety Concern:

The potential public health impact of CHF related to EPREX treatment is unknown.

Evidence Source:

Information regarding clinical trials is provided in Annex 4.

Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report with data cutoff of 30 June 2015.

Bárány 2007; CHMP Response 2014; Cullen 2011; Della Porta 2011; Goldberg 2010; Khakoo 2008; Lisowska 2004; Mayo Clinic, 2015: cancer; Mayo Clinic, 2015: heart failure; Memtsoudis 2011; Nanda 2009; Overbeek 2012; Patnaik 2011; Pavia 2007; Schiffrin 2007; Senkus 2011; Zöller 2012

MedDRA Terms:

Cardiac Failure SMQ; scope=narrow and broad

SVII.4. Identified and Potential Interactions

SVII.4.1. Overview of Potential for Interactions

Epoetin alfa increases RBC maturation and RBC count in animals and humans. Although no formal drug interaction studies have been conducted with epoetin alfa and drugs that affect erythropoiesis, caution should be exercised in the concomitant use of drugs known to affect erythropoiesis because they may impact the response to epoetin alfa, such as an increase in the number of erythrocytes, HGB values, reticulocyte counts, and iron-incorporation rate.

There is no evidence indicating that treatment with epoetin alfa alters the metabolism of other drugs. However, because cyclosporine is bound by RBCs, there is potential for decreased serum levels of cyclosporine when used with epoetin alfa. The SmPC addresses the need to monitor blood levels of cyclosporine and adjust cyclosporine dose as necessary when cyclosporine is given concomitantly with epoetin alfa (SmPC Section 4.5).

A drug interaction trial (Trial EPO-PHI-383) was conducted in women with metastatic breast cancer to evaluate the effect of a single 40,000-IU SC dose of EPREX on the steady-state pharmacokinetic parameters of trastuzumab (6 mg/kg every 3 weeks). The trial demonstrated that co-administration of EPREX had no effect on the pharmacokinetics of trastuzumab (EPREX IB 2012).

Detailed metabolic degradation studies with EPREX have not been conducted, and the major routes of elimination have not been determined. However, measurement of epoetin alfa following IV administration demonstrated 10% excretion by the kidneys. In normal volunteers, the half-life of IV-administered EPREX is approximately 20% shorter than the half-life in patients with CRF. Therefore, caution should be exercised in the concomitant use of EPREX with drugs that are known to interfere with renal function.

The safety and optimal dosage regimen of EPREX have not been established in the presence of hepatic dysfunction. However, due to decreased metabolism, patients with hepatic dysfunction may have increased erythropoiesis with EPREX. Therefore, EPREX should also be used with caution in patients with chronic liver failure.

To date, there are no identified important interactions with medicinal products, food, herbs, and other substances.

SVII.4.2. Important Identified and Potential Interactions

Cyclosporin	
Effect of interaction	Concomitant use of epoetin alfa with cyclosporin theoretically could decrease serum cyclosporin levels and, therefore, increase the risk of renal transplant rejection.
Evidence source	Freeman, 1991
Possible mechanisms	Epoetin alfa increases RBC maturation, thereby increasing RBC count. Because cyclosporin binds to RBCs, there is a resultant potential for decreased serum levels of cyclosporin when used with epoetin alfa.
Potential health risk	Increased risk of renal transplant rejection MedDRA preferred terms: drug interaction, acute graft versus host disease, graft versus host disease, kidney transplant rejection, transplant rejection
Discussion	Although there is a theoretical risk for a drug interaction with cyclosporin, an actual risk has not been identified.

MedDRA=Medical Dictionary for Regulatory Activities; RBC=red blood cell

SVII.5. Pharmacologic Class Effects

Established risks with other ESAs that are considered to be important identified or potential risks with EPREX include:

- Thrombotic vascular events
- Pure red cell aplasia
- Hypertension/Hypertensive crisis
- Disease progression
- Survival impact

Risks that are considered to be pharmacologic class effects and are also important identified or potential risks with EPREX are characterised in Module SVII.3; the frequencies of these risks seen with the EPREX compared with those seen with other products in the same or similar pharmacologic class are presented in Module SVII.5.1

SVII.5.1. Pharmacologic Class Risks Already Included as Important Identified or Potential Risks

Risk (MedDRA preferred term)	Frequency: In Clinical Trials of EPREX*	With Other Products in Same Class Source of data / journal reference: SmPC†
Thrombotic Vascular Events	An increased incidence of thromboembolic events (including the following terms listed in Section 4.8 of the SmPC: arterial and venous, fatal and non-fatal events, such as DVT, pulmonary emboli, retinal thrombosis, arterial thrombosis (including MI), cerebrovascular accidents, (including cerebral infarction and cerebral haemorrhage), transient ischaemic attacks, and shunt thrombosis (including dialysis equipment), and thrombosis within arteriovenous shunt aneurisms) has been reported in patients receiving ESAs, including epoetin alfa (SmPC Sections 4.4 and 4.8). Frequency is considered "common" (≥1/100 to <1/10 cases per patient) as stated in Section 4.8 of the SmPC.	Aranesp: Thromboembolic events (Uncommon for patients with CRF, common for patients with cancer) Binocrit: Same language as EPREX Eporatio: Thromboembolic events (Not known) NeoRecormon: Thromboembolic events (Common for patients with cancer) Silapo: An increased incidence of thromboembolic events has been observed in patients receiving erythropoietic agents
Pure Red Cell Aplasia	Antibody-mediated PRCA has been very rarely reported in <1/10,000 cases per PY after months to years of treatment with EPREX (SmPC Section 4.8).	Aranesp: PRCA (Not known-isolated cases reported) Binocrit: PRCA (Not known) Eporatio: PRCA (isolated cases) NeoRecormon: (isolated cases) Silapo: (Frequency not known-cases have been very rarely reported in patients with CRF)

Risk (MedDRA preferred term)	Frequency: In Clinical Trials of EPREX*	With Other Products in Same Class Source of data / journal reference: SmPC†
Hypertension/Hypertensive crisis	Hypertension is considered "common" (≥1/100 to <1/10 cases per patient) as stated in Section 4.8 of the SmPC. Hypertensive crisis with encephaolopathy and seizures, requiring immediate attention of a physician and intensive medical care, have occurred during epoetin alfa treatment in patients with previously normal or low blood pressure (SmPC Sections 4.4 and 4.8).	Aranesp: Hypertension (very common) Binocrit: Hypertension (common) Eporatio: Hypertension (common) NeoRecormon: Hypertension (common) Silapo: Hypertension may occur in epoetin alfa-treated patients. The most frequent adverse reaction during treatment with epoetin alfa is a dose-dependent increase in blood pressure or aggravation of existing hypertension
Disease Progression	In controlled clinical trials, use of EPREX, ERYPO, and other ESAs have demonstrated shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a HGB of 12 to 14 g/dL (7.5 to 8.7 mmol/l) (SmPC Section 4.4). Decreased locoregional control in patients with advanced head and neck cancer receiving radiation therapy when administered to achieve a HGB concentration level of greater than 14 g/dL (8.7 mmol/l) has also been observed (SmPC Section 4.4).	Aranesp: Same language as EPREX Binocrit: Same language as EPREX Eporatio: Same language as EPREX NeoRecormon: Same language as EPREX Silapo: Same as language EPREX

Risk (MedDRA preferred term)	Frequency: In Clinical Trials of EPREX*	With Other Products in Same Class Source of data / journal reference: SmPC†
Survival Impact	In controlled clinical trials, use of EPREX, ERYPO, and other ESAs increased the risk of death when administered to achieve a HGB concentration of 12 g/dL (7.5 mmol/L) in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. 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 HGB concentration range of 12 to 14 g/dL (7.5 to 8.7 mmol/L) has also been observed (SmPC Section 4.4). Erythropoiesis-stimulating agents are not indicated for use in this patient population.	Aranesp: Same language as EPREX Binocrit: Same language as EPREX Eporatio: Same language as EPREX NeoRecormon: Same language as EPREX Silapo: Same language as EPREX

ADR=adverse drug reaction; CKD=chronic kidney disease; CNS=central nervous system; CRF=chronic renal failure; DVT=deep venous thrombosis; ESA=erythropoiesis-stimulating agent; HGB=haemoglobin; MedDRA=Medical Dictionary for Regulatory Activities; MI=myocardial infarction; PRCA=pure red cell aplasia; PY=patient years; SmPC=Summary of Product Characteristics

* Incidence of ADRs

† Aranesp SmPC 2013, Binocrit SmPC 2013, Eporatio SmPC 2013, NeoRecormon 2012, Silapo 2012

SVII.5.2. Important Pharmacologic Class Effects That Are NOT Considered to be Important Identified or Potential Risks

There are no important pharmacologic class effects that are not considered to be important identified or potential risks with EPREX.

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

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Active substance	Epoetin alfa
Product(s) concerned	EPREX ERYPO ERYPO FS
MAH/MAA name	Janssen-Cilag Pharma GmbH, Austria JANSSEN-CILAG GmbH, Germany Janssen-Cilag NV, Belgium Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag International NV, Cyprus Janssen-Cilag s.r.o., Czech Republic Janssen-Cilag A/S, Denmark Janssen-Cilag OY, Finland JANSSEN-CILAG, France Janssen-Cilag Pharmaceutical S.A.C.I., Greece Janssen-Cilag Limited Janssen-Cilag SpA, Italy Janssen-Cilag, NV, Luxembourg Janssen-Cilag International NV, Malta Janssen-Cilag BV, Netherlands Janssen-Cilag AS, Norway Janssen-Cilag Farmaceutica, Lda, Portugal Janssen-Cilag S.A. Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag S.A., Spain Janssen-Cilag AB, Sweden Janssen-Cilag Ltd, United Kingdom

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Summary of Safety Concerns	
Important identified risks	Thrombotic vascular events Pure red cell aplasia Hypertension/Hypertensive crisis
Important potential risks	Disease progression Survival impact Congestive heart failure
Missing information	None

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

PART III: PHARMACOVIGILANCE PLAN

Active substance	Epoetin alfa
Product(s) concerned	EPREX ERYPO ERYPO FS
MAH/MAA name	Janssen-Cilag Pharma GmbH, Austria JANSSEN-CILAG GmbH, Germany Janssen-Cilag NV, Belgium Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag International NV, Cyprus Janssen-Cilag s.r.o., Czech Republic Janssen-Cilag A/S, Denmark Janssen-Cilag OY, Finland JANSSEN-CILAG, France Janssen-Cilag Pharmaceutical S.A.C.I., Greece Janssen-Cilag Limited Janssen-Cilag SpA, Italy Janssen-Cilag, NV, Luxembourg Janssen-Cilag International NV, Malta Janssen-Cilag BV, Netherlands Janssen-Cilag AS, Norway Janssen-Cilag Farmaceutica, Lda, Portugal Janssen-Cilag S.A. Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag S.A., Spain Janssen-Cilag AB, Sweden Janssen-Cilag Ltd, United Kingdom

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The pharmacovigilance actions planned in response to each safety concern are summarised in the following table.

III.1. Safety Concerns and Overview of Planned Pharmacovigilance Actions

Safety Concern Areas requiring confirmation or further investigation	Proposed routine and additional pharmacovigilance activities	Objectives
Important Identified Risks		
Thrombotic Vascular Events 1. Monitor reporting rates 2. Evaluate risk factors	• Ongoing monitoring with routine pharmacovigilance activities • Additional: Trial EPO-ANE-3010	Routine evaluation of the risk Evaluate the incidence of TVEs in a randomised, open-label, multicentre, Phase 3 trial of EPREX plus standard supportive care versus standard supportive care alone in anaemic patients with metastatic breast cancer receiving standard chemotherapy
Pure Red Cell Aplasia 1. Monitor reporting rates 2. Evaluate risk factors	• Ongoing monitoring with routine pharmacovigilance activities • Additional: Semiannual Immunogenicity Report; Independent Safety Advisory Committee adjudication (ISAC); PRCA pharmacovigilance plan	Routine monitoring of the risk Estimate the incidence of anti-human erythropoietin Ab and anti-erythropoietin PRCA in patients with SC exposure to ESAs
Hypertension/Hypertensive crisis 1. Monitor reporting rates 2. Evaluate risk factors	• Ongoing monitoring with routine pharmacovigilance activities	Routine evaluation of the risk
Important Potential Risks		
Disease Progression 1. Monitor reporting rates 2. Evaluate risk factors	• Ongoing monitoring with routine pharmacovigilance activities • Additional: Trial EPO-ANE-3010	Routine evaluation of the risk Evaluate the occurrence of disease progression in a randomised, open-label, multicentre, Phase 3 trial of EPREX plus standard supportive care versus standard supportive care alone in anaemic patients with metastatic breast cancer receiving standard chemotherapy
Survival Impact 1. Monitor reporting rates 2. Evaluate risk factors	• Ongoing monitoring with routine pharmacovigilance activities • Additional: Trial EPO-ANE-3010	Routine evaluation of the risk Evaluate the survival impact in a randomised, open-label, multicentre, Phase 3 trial of EPREX plus standard supportive care versus standard supportive care alone in anaemic patients with metastatic breast cancer receiving standard chemotherapy
Congestive Heart Failure 1. Monitor reporting rates 2. Evaluate risk factors	• Ongoing monitoring with routine pharmacovigilance activities	Routine evaluation of the risk

Safety Concern Areas requiring confirmation or further investigation	Proposed routine and additional pharmacovigilance activities	Objectives

Ab=antibody; ESA=erythropoiesis-stimulating agent; PRCA=pure red cell aplasia; SC=subcutaneous; TVE=thrombotic vascular event

III.2. Additional Pharmacovigilance Activities to Assess the Effectiveness of Risk Minimisation Measures

There are no additional pharmacovigilance activities being performed specifically to measure the effectiveness of the risk minimisation measures for EPREX.

III.3. Studies and Other Activities Completed Since the Last Update of the Pharmacovigilance Plan

A CSR for Trial EPO-ANE-3010 has been completed given that the number of PFS events reached the target of 1,650 events for the analysis of the primary endpoint. A final analysis for survival will be performed after 1,650 patients have died. As of the clinical cutoff date of 07 July 2014 for the CSR, 1,337 deaths have been reported.

III.4. Details of Outstanding Additional Pharmacovigilance Activities

III.4.1. Imposed Mandatory Additional Pharmacovigilance Activity (Key to Benefit-Risk)

No imposed mandatory additional pharmacovigilance activities are planned or ongoing for EPREX.

III.4.2. Mandatory Additional Pharmacovigilance Activity (Being a Specific Obligation)

No mandatory additional pharmacovigilance activities are planned or ongoing for EPREX.

III.4.3. Required Additional Pharmacovigilance Activities to Address Specific Safety Concerns or to Measure Effectiveness of Risk Minimisation Measures

Required Additional Pharmacovigilance Activities

	Description of activity (or study title if known)	Milestone(s)	Due Date(s)
1.	Trial EPO-ANE-3010 (A Randomised, Open-Label, Multicentre, Phase 3 Study of Epoetin Alfa Plus Standard Supportive Care Versus Standard Supportive Care in Anemic Patients With Metastatic Breast Cancer Receiving Standard Chemotherapy)	Final report for OS	4Q 2017

OS=overall survival.

III.4.4. Stated Additional Pharmacovigilance Activities

No stated additional pharmacovigilance activities are planned or ongoing for EPREX.

III.5. Summary of the Pharmacovigilance Plan

III.5.1. Table of Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan

Study ID/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Trial EPO-ANE-3010 Randomised, Open-Label, Multicentre, Phase 3 Study of Epoetin Alfa Plus Standard Supportive Care Versus Standard Supportive Care in Anemic Patients With Metastatic Breast Cancer Receiving Standard Chemotherapy Category 3	Assess the impact on tumour progression and TVEs, in terms of PFS, of EPREX plus standard-of-care compared with standard-of-care alone (packed RBC transfusions), when used to treat anaemia in patients with metastatic breast cancer receiving first-line or second-line chemotherapy.	Disease progression; TVEs, survival impact	Ongoing	Final report for OS in 4Q 2017

OS=overall survival; PFS=progression-free survival; RBC=red blood cell; TVE=thrombotic vascular event.

III.5.2. Table of Completed Studies/Activities From the Pharmacovigilance Plan

Study ID/Protocol (activity type, title and category [1-3])	Objectives	Safety concerns addressed	Status	Date of submission of interim or final study report
Trial EPO-ANE-4014 Prospective, Immunogenicity Surveillance Registry to Estimate the Incidence of Erythropoietin Antibody-Mediated Pure Red Cell Aplasia Among Subjects With Chronic Renal Failure and Subcutaneous Exposure to Recombinant Erythropoietin Products Category 2	Estimate IR of erythropoietin Ab-mediated PRCA with SC exposure to PS-80 formulation of EPREX and compare with that of other currently marketed ESAs with adjustment for duration of exposure	PRCA	Completed	Final study report submitted 25 Jan 2012
Trial EPO-ANE-4008 A randomised, open-label, multicentre study evaluating thrombovascular events in subjects with cancer receiving chemotherapy and administered epoetin alfa once or 3 times a week for the treatment of anaemia Category 2	Further evaluate the safety profile of the QW dosing regimen in patients with cancer, with particular focus on the incidence of TVEs	TVEs	Completed	Final study report submitted 31 Mar 2010
Trial EPOANE4076[a] A Prospective, Immunogenicity Surveillance Registry of Erythropoiesis-Stimulating Agents with Subcutaneous Exposure in Thailand Category 3	Estimate the incidence of anti-human erythropoiesis and anti-erythropoietin PRCA in patients using any ESA by the SC route.	PRCA	Completed	Final report submitted 05 May 2015

Ab=antibody; ESA=erythropoiesis-stimulating agent; IR=incidence rate; MAH=market authorisation holder; PRCA=pure red cell aplasia; PRIMS=Pharmacoepidemiology Registry EPO-ANE-4014 Prospective Immunogenicity Surveillance; PS-80=polysorbate-80; QW=once weekly; SC=subcutaneous; TVE=thrombotic vascular event

[a]Trial EPOANE4076 was being conducted by the collaboration among Nephrology Society of Thailand, the Thai Society of Haematology, the Association of Hospital Pharmacy (Thailand), and the Adverse Product Reaction Monitoring Center of the Food and Drug Administration Thailand, and not by the MAH. The final report was prepared by the principal investigator.

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

PART IV: PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

Active substance	Epoetin alfa
Product(s) concerned	EPREX ERYPO ERYPO FS
MAH/MAA name	Janssen-Cilag Pharma GmbH, Austria JANSSEN-CILAG GmbH, Germany Janssen-Cilag NV, Belgium Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag International NV, Cyprus Janssen-Cilag s.r.o., Czech Republic Janssen-Cilag A/S, Denmark Janssen-Cilag OY, Finland JANSSEN-CILAG, France Janssen-Cilag Pharmaceutical S.A.C.I., Greece Janssen-Cilag Limited Janssen-Cilag SpA, Italy Janssen-Cilag, NV, Luxembourg Janssen-Cilag International NV, Malta Janssen-Cilag BV, Netherlands Janssen-Cilag AS, Norway Janssen-Cilag Farmaceutica, Lda, Portugal Janssen-Cilag S.A. Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag S.A., Spain Janssen-Cilag AB, Sweden Janssen-Cilag Ltd, United Kingdom

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IV.1 Applicability of Efficacy to All Patients in the Target Population

EPREX has been approved in numerous countries worldwide for the treatment of anaemia in patients with CRF (on dialysis and predialysis) and anaemia and reduction of transfusion requirements in adult patients with cancer receiving chemotherapy. It has also been approved in several countries as a facilitator of autologous blood predonation and to reduce allogeneic blood requirements in the perisurgical setting. The first approval, in 1988, was in the CRF setting. Over the course of the clinical development programme, the efficacy of EPREX has been studied in 15,339 patients in clinical trials with over 94,000 person-months of exposure. Over 200 patients have been treated in clinical trials for ≥24 months and thus, the long-term efficacy of EPREX has been well documented.

Forty-two percent of patients in the clinical trials were aged 65 years or older and 17% were aged 75 years or older. However, epoetin alfa has been shown to be efficacious in the paediatric populations for CRF (dialysis) and CIA, and there is no mention of age-related effects on efficacy in the SmPC.

A majority of patients (69%) were White, while 13% were Black and 9% were Asian, Hispanic, or of a mixed race (data on ethnic and racial origin were missing for 10% of patients). The efficacy and safety of EPREX in clinical trials has led to its approval in multiple Latin American and Asian countries; therefore, there is no reason to suggest differences in the efficacy of EPREX in any particular ethnic or racial subgroup.

IV.2. Tables of Postauthorisation Efficacy Studies

There are no postauthorisation efficacy trials planned or currently ongoing with the use of EPREX.

IV.3. Summary of the Postauthorisation Efficacy Development Plan

There are no postauthorisation efficacy trials planned or currently ongoing with the use of EPREX.

IV.4. Summary of Completed Postauthorisation Efficacy Studies

No efficacy studies were required postauthorisation.

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

PART V: RISK MINIMISATION MEASURES

Active substance	Epoetin alfa
Product(s) concerned	EPREX ERYPO ERYPO FS
MAH/MAA name	Janssen-Cilag Pharma GmbH, Austria JANSSEN-CILAG GmbH, Germany Janssen-Cilag NV, Belgium Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag International NV, Cyprus Janssen-Cilag s.r.o., Czech Republic Janssen-Cilag A/S, Denmark Janssen-Cilag OY, Finland JANSSEN-CILAG, France Janssen-Cilag Pharmaceutical S.A.C.I., Greece Janssen-Cilag Limited Janssen-Cilag SpA, Italy Janssen-Cilag, NV, Luxembourg Janssen-Cilag International NV, Malta Janssen-Cilag BV, Netherlands Janssen-Cilag AS, Norway Janssen-Cilag Farmaceutica, Lda, Portugal Janssen-Cilag S.A. Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag S.A., Spain Janssen-Cilag AB, Sweden Janssen-Cilag Ltd, United Kingdom

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V.1. Risk Minimisation Measures by Safety Concern

The Company has not identified any risk minimisation activities needed beyond those already outlined in the current SmPC. The Company continues its ongoing pharmacovigilance and will assess the need for any risk minimisation actions as new data emerges.

Important Identified Risks	
Safety Concern 1: Thrombotic vascular events	
Objective(s) of the risk minimisation measures	Advise regarding the risk of TVEs and provide guidance on ways to minimise the risk of TVEs.
Routine risk minimisation measures	The increased risk of TVEs is described in Sections 4.4 and 4.8 of the SmPC. For patients with cancer, EPREX should be administered by the SC route with dose adjustments to maintain HGB concentrations between 10 to 12g/dL. Section 4.2 of the SmPC provides guidance for appropriate dose adjustment when HGB values exceed 12 g/dL and to ensure that the lowest approved dose is used. EPREX is contraindicated in surgery patients who cannot receive such prophylaxis (SmPC Section 4.3). Thrombosis prophylaxis is recommended in high-risk patients (SmPC Section 4.4). EPREX is not recommended in perisurgery patients with a baseline HGB >13 g/dL (SmPC Section 4.4). Section 4.4 of the SmPC advises that HGB levels should be closely monitored due to a potential increased risk of TVEs and fatal outcomes when patients are treated at above-target HGB levels. An increased incidence of TVEs has been observed in patients receiving ESAs (SmPC Section 4.8); this risk should be weighed against the benefit from treatment with EPREX, particularly in patients at increased risk of TVEs, such as obese patients and patients with a prior history of TVEs (eg, DVT or pulmonary embolism) (SmPC Section 4.4).
Additional risk minimisation measure(s)	Based on the risk assessment, the MAH believes the language included in the SmPC, along with the Pharmacovigilance Plan are sufficient tools to manage the risk for patients treated with EPREX. Therefore, no additional risk minimisation activities are proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Spontaneous and literature reports review
Criteria for judging the success of the proposed risk minimisation measures	Stable reporting trend analysis of postmarketing data
Planned dates for assessment	At the end of each PBRER/PSUR reporting interval.
Results of effectiveness measurement	Stable reporting observed
Impact of risk minimisation	Achieving aim of stable reporting in postmarketing surveillance

Comment	The MAH will continue to monitor TVEs.
Safety Concern 2: Pure Red Cell Aplasia	
Objective(s) of the risk minimisation measures	Advise regarding the risk of PRCA and provide guidance on ways to minimise the risk of PRCA.
Routine risk minimisation measures	Intravenous administration should be used when possible. Where IV access is not readily available, EPREX may be administered subcutaneously (SmPC Section 4.2). The use of EPREX is contraindicated in patients who develop PRCA following treatment with any ESA (SmPC Section 4.3). Physicians are advised of the incidence of PRCA and measures that can be taken to diagnose PRCA in Sections 4.4 and 4.8 of the SmPC. In patients developing sudden lack of efficacy defined by a decrease in HGB (1 to 2 g/dL per month) with increased need for transfusions, a reticulocyte count should be obtained and typical causes of non-response (eg, iron, folate or vitamin B12 deficiency, aluminium intoxication, infection or inflammation, blood loss and haemolysis) should be investigated. (See Section 4.4 of the SmPC).
Additional risk minimisation measure(s)	Based on the risk assessment, the MAH believes the language included in the SmPC, along with the Pharmacovigilance Plan are sufficient tools to manage the risk for patients treated with EPREX. Therefore, no additional risk minimisation activities are proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Spontaneous and literature reports review
Criteria for judging the success of the proposed risk minimisation measures	Stable reporting trend analysis of postmarketing data
Planned dates for assessment	At the end of each PBRER/PSUR reporting interval
Results of effectiveness measurement	Stable reporting observed
Impact of risk minimisation	Achieving aim of stable reporting of erythropoietin Ab-mediated PRCA in postmarketing surveillance
Comment	The MAH will continue to monitor PRCA.

Safety Concern 3: Hypertension/Hypertensive crisis	
Objective(s) of the risk minimisation measures	Advise regarding the risk of hypertension and provide guidance on ways to minimise the risk of hypertension.
Routine risk minimisation measures	The use of EPREX is contraindicated in patients with uncontrolled hypertension (SmPC Section 4.3). Sections 4.4 and 4.8 of the SmPC state that blood pressure should be closely monitored and controlled as necessary. Epoetin alfa should be used with caution in the presence of untreated, inadequately treated, or poorly controllable hypertension. It may be necessary to add or increase antihypertensive treatment. If blood pressure cannot be controlled, epoetin alfa treatment should be discontinued (SmPC Section 4.4). Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have occurred also during epoetin alfa treatment in patients with previously normal or low blood pressure. Particular attention should be paid to sudden stabbing migraine-like headaches as a possible warning signal (see SmPC Sections 4.4 and 4.8).
Additional risk minimisation measure(s)	Based on the risk assessment, the MAH believes the language included in the SmPC, along with the Pharmacovigilance Plan are sufficient tools to manage the risk for patients treated with EPREX. Therefore, no additional risk minimisation activities are proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Spontaneous and literature reports review
Criteria for judging the success of the proposed risk minimisation measures	Stable reporting trend analysis of postmarketing data
Planned dates for assessment	At the end of each PBRER/PSUR reporting interval
Results of effectiveness measurement	Stable reporting observed
Impact of risk minimisation	Achieving aim of stable reporting in postmarketing surveillance
Comment	The MAH will continue to monitor hypertension.

Important Potential Risks	
Safety Concern 4: Disease Progression	
Objective(s) of the risk minimisation measures	Advise regarding the risk of disease progression and provide guidance on ways to minimise the risk of disease progression.
Routine risk minimisation measures	Section 4.4 of the SmPC addresses the potential for tumour growth progression with the administration of ESAs and demonstrated increased mortality in patients with head and neck cancer and breast cancer when administered to target a HGB concentration of 12 to 14 g/dL (7.5 to 8.7 mmol/L). When used according to labelled guidance for correction of anaemia in the setting of CIA, there is no evidence that epoetin alfa has an adverse effect on disease progression. The SmPC only indicates treatment in those patients receiving concomitant chemotherapy, and as such, is not indicated in patients with cancer-induced anaemia who are not receiving concomitant chemotherapy, or are receiving radiotherapy only. Epoetin alfa should be discontinued in non-responding patients (SmPC Section 4.2).
Additional risk minimisation measure(s)	Based on the risk assessment, the MAH believes the language included in the SmPC, along with the Pharmacovigilance Plan are sufficient tools to manage the risk for patients treated with EPREX. Therefore, no additional risk minimisation activities are proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Spontaneous and literature reports review
Criteria for judging the success of the proposed risk minimisation measures	Stable reporting trend analysis of postmarketing data
Planned dates for assessment	At the end of each PBRER/PSUR reporting interval
Results of effectiveness measurement	Stable reporting observed
Impact of risk minimisation	Achieving aim of stable reporting in postmarketing surveillance
Comment	The MAH will continue to monitor disease progression.

Safety Concern 5: Survival Impact	
Objective(s) of the risk minimisation measures	Advise regarding the risk of impact on survival and provide guidance on ways to minimise the risk of death.
Routine risk minimisation measures	Sections 4.4 and 5.1 of the SmPC address the risk of survival impact. When used according to labelled guidance for correction of anaemia in the setting of CIA, there is no evidence that epoetin alfa has an adverse effect on survival. However, the data strongly suggest that epoetin alfa treatment increases the risk of death and serious cardiovascular events when administered to target HGB >12 g/dL (SmPC Section 4.4). The SmPC advises that the target HGB should be up to 12 g/dL. Dose adjustments should be made to maintain HGB concentrations between 10 to 12g/dL. A sustained HGB level of greater than 12g/dL should be avoided; guidance for appropriate dose adjustment for when HGB values exceed 12 g/dL is also described in Section 4.2 of the SmPC. Patients should be monitored closely to ensure that the lowest approved dose of ESA is used to provide adequate control of symptoms of anaemia. In order to prevent HGB concentration from exceeding the recommended target (12 g/dL) or rising too rapidly (greater than 1 g/dL in 2 weeks), the guidelines for dose and frequency of dose adjustments should be followed (SmPC Section 4.2).
Additional risk minimisation measure(s)	Based on the risk assessment, the MAH believes the language included in the SmPC, along with the Pharmacovigilance Plan are sufficient tools to manage the risk for patients treated with EPREX. Therefore, no additional risk minimisation activities are proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Spontaneous and literature reports review
Criteria for judging the success of the proposed risk minimisation measures	Stable reporting trend analysis of postmarketing data
Planned dates for assessment	At the end of each PBRER/PSUR reporting interval
Results of effectiveness measurement	Stable reporting observed
Impact of risk minimisation	Achieving aim of stable reporting in postmarketing surveillance
Comment	The MAH will continue to monitor survival impact.

Safety Concern 6: Congestive Heart Failure	
Objective(s) of the risk minimisation measures	Advise regarding the risk of CHF and provide guidance on ways to minimise the risk of CHF.
Routine risk minimisation measures	The target HGB should be up to 12 g/dL and should not be exceeded (SmPC Section 4.4). Physicians are also warned that HGB levels greater than 12 g/dL may be associated with a higher risk of cardiovascular events in patients with CRF (SmPC Section 4.4).
Additional risk minimisation measure(s)	Based on the risk assessment, the MAH believes the language included in the SmPC, along with the Pharmacovigilance Plan are sufficient tools to manage the risk for patients treated with EPREX. Therefore, no additional risk minimisation activities are proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Spontaneous and literature reports review
Criteria for judging the success of the proposed risk minimisation measures	Stable reporting trend analysis of postmarketing data
Planned dates for assessment	At the end of each PBRER/PSUR reporting interval
Results of effectiveness measurement	Stable reporting observed
Impact of risk minimisation	Achieving aim of stable reporting in postmarketing surveillance
Comment	The MAH will continue to monitor CHF.

Ab=antibody; CHF=congestive heart failure; CIA=chemotherapy-induced anaemia; CNS=central nervous system; CRF=chronic renal failure; DVT=deep vein thrombosis; ESA=erythropoiesis-stimulating agent; HGB=haemoglobin; IV=intravenous; MAH=marketing authorisation holder; PRCA=pure red cell aplasia; PBRER/PSUR=Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report; SC=subcutaneous; SmPC=Summary of Product Characteristics; TVE=thrombotic vascular event

V.2. Risk Minimisation Measure Failure

No risk minimisation measure has been judged to have failed to date.

V.3. Summary Table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important identified risks:		
Thrombotic vascular events	The increased risk of TVEs is described in SmPC Sections 4.4 and 4.8. Patients with cancer being treated for CIA should be monitored closely to ensure that the lowest approved dose of ESA is used to provide adequate control of symptoms of anaemia. Haemoglobin values should not be allowed to rise above 12 g/dL (SmPC Sections 4.2 and 4.4). Thrombosis prophylaxis for TVEs in high-risk patients is also recommended (SmPC Section 4.4) and EPREX is contraindicated in surgery patients who for any reason cannot receive antithrombotic prophylaxis (SmPC Section 4.3). The use of EPREX is also not recommended in perisurgery patients with a baseline HGB >13 g/dL (SmPC Section 4.4).	None
Pure red cell aplasia	Intravenous administration should be used when possible. Where IV access is not readily available, EPREX may be administered subcutaneously (SmPC Section 4.2). Physicians are advised of the incidence of PRCA and measures that can be taken to diagnose PRCA, as stated in Sections 4.4 and 4.8 of the SmPC. The use of EPREX is contraindicated in patients who develop PRCA following treatment with any ESA (SmPC Section 4.3).	None
Hypertension/Hypertensive crisis	The use of EPREX is contraindicated in patients with uncontrolled hypertension (SmPC Section 4.3). Blood pressure should be closely monitored and controlled as necessary (SmPC Sections 4.4 and 4.8). EPREX should be used with caution in the presence of untreated, inadequately treated or poorly controllable hypertension. It may be necessary to add or increase antihypertensive treatment. If blood pressure cannot be controlled, EPREX treatment should be discontinued (SmPC Section 4.4).	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important potential risks:		
Disease progression	When used according to labelled guidance for correction of anaemia in the setting of CIA, there is no evidence that epoetin alfa has an adverse effect on disease progression. However, the data suggest that ESA treatment may increase mortality in patients with head and neck cancer and breast cancer when administered to a target HGB concentration of 12 to 14 g/dL (SmPC Section 4.4). Epoetin alfa should be discontinued in non-responding patients (SmPC Section 4.2).	None
Survival impact	When used according to labelled guidance for correction of anaemia in the setting of CIA, there is no evidence that epoetin alfa has an adverse effect on survival. However, the data suggest that epoetin alfa treatment increases the risk of death and serious cardiovascular events when administered to a target HGB concentration >12 g/dL (SmPC Sections 4.4 and 5.1); therefore, the target HGB concentration of 12 g/dL should not to be exceeded (SmPC Section 4.4). Patients should be monitored closely to ensure that the lowest approved dose of ESA is used to provide adequate control of symptoms of anaemia. Guidelines for dose and frequency of dose adjustments should be followed (SmPC Section 4.2)	None
Congestive heart failure	The target HGB should be up to 12 g/dL and should not be exceeded. Haemoglobin concentrations >12 g/dL may be associated with a higher risk of cardiovascular events in patients with CRF (SmPC Section 4.4).	None

CIA=chemotherapy-induced anaemia; CNS=central nervous system; CRF=chronic renal failure; ESA=erythropoiesis-stimulating agent; HGB=haemoglobin; IV=intravenous; PRCA=pure red cell aplasia; SmPC=Summary of Product Characteristics; TVE=thrombotic vascular events

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EPREX (epoetin alfa)

PART VI: SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY PRODUCT

Active substance	Epoetin alfa
Product(s) concerned	EPREX ERYPO ERYPO FS
MAH/MAA name	Janssen-Cilag Pharma GmbH, Austria JANSSEN-CILAG GmbH, Germany Janssen-Cilag NV, Belgium Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag International NV, Cyprus Janssen-Cilag s.r.o., Czech Republic Janssen-Cilag A/S, Denmark Janssen-Cilag OY, Finland JANSSEN-CILAG, France Janssen-Cilag Pharmaceutical S.A.C.I., Greece Janssen-Cilag Limited Janssen-Cilag SpA, Italy Janssen-Cilag, NV, Luxembourg Janssen-Cilag International NV, Malta Janssen-Cilag BV, Netherlands Janssen-Cilag AS, Norway Janssen-Cilag Farmaceutica, Lda, Portugal Janssen-Cilag S.A. Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria Janssen-Cilag S.A., Spain Janssen-Cilag AB, Sweden Janssen-Cilag Ltd, United Kingdom

Data lock point for this module	20 December 2017
Version number of RMP when this module was last updated	5.4

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VI.1. Elements for Summary Tables in the EPAR

VI.1.1. Summary Table of Safety Concerns

Important identified risks	Thrombotic vascular events
	Pure red cell aplasia
	Hypertension/Hypertensive crisis
Important potential risks	Disease progression
	Survival impact
	Congestive heart failure
Missing information	None

VI.1.2. Table of Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Trial EPO-ANE-3010 Randomised, Open-Label, Multicentre, Phase 3 Study of Epoetin Alfa Plus Standard Supportive Care Versus Standard Supportive Care in Anaemic Patients With Metastatic Breast Cancer Receiving Standard Chemotherapy Category 3	Assess the impact on tumour progression and TVEs, in terms of PFS, of EPREX plus standard-of-care compared with standard-of-care alone (packed RBC transfusions), when used to treat anaemia in patients with metastatic breast cancer receiving first-line or second-line chemotherapy	Disease progression; TVE, survival impact	Ongoing	Final report for OS in 4Q 2017

MAH=market authorisation holder; OS=overall survival; PFS=progression-free survival; RBC=red blood cell; TVE=thrombotic vascular event
[a] Note: Trial EPOANE4076 is being conducted by the Nephrology Society of Thailand and not by the MAH.

VI.1.3. Summary of Postauthorisation Efficacy Development Plan

No efficacy trials were required postauthorisation.

VI.1.4. Summary Table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important identified risks		
Thrombotic vascular events	The increased risk of TVEs is described in Sections 4.4 and 4.8 of the SmPC. Patients with cancer being treated for CIA should be monitored closely to ensure that the lowest approved dose of ESA is used to provide adequate control of symptoms of anaemia. Haemoglobin values should not be allowed to rise above 12 g/dL (SmPC Sections 4.2 and 4.4). Thrombosis prophylaxis for TVEs in high-risk patients is also recommended (SmPC Section 4.4) and EPREX is contraindicated in surgery patients who for any reason cannot receive anti-thrombotic prophylaxis (SmPC Section 4.3). The use of EPREX is also not recommended in perisurgery patients with a baseline HGB >13 g/dL (SmPC Section 4.4).	None
Pure red cell aplasia	Intravenous administration should be used when possible. Where IV access is not readily available, EPREX may be administered subcutaneously (SmPC Section 4.2). Physicians are advised of the incidence of PRCA and measures that can be taken to diagnose PRCA, as stated in Sections 4.4 and 4.8 of the SmPC. The use of EPREX is contraindicated in patients who develop PRCA following treatment with any ESA (SmPC Section 4.3).	None
Hypertension/hypertensive crisis	The use of EPREX is contraindicated in patients with uncontrolled hypertension (SmPC Section 4.3). Blood pressure should be closely monitored and controlled as necessary (SmPC Sections 4.4 and 4.8). EPREX should be used with caution in the presence of untreated, inadequately treated, or poorly controllable hypertension. It may be necessary to add or increase antihypertensive treatment. If blood pressure cannot be controlled, EPREX treatment should be discontinued (SmPC Section 4.4).	None

Important potential risks		
Disease progression	When used according to labelled guidance for correction of anaemia in the setting of CIA, there is no evidence that epoetin alfa has an adverse effect on disease progression. However, the data suggest that ESA treatment may increase mortality in patients with head and neck cancer and breast cancer when administered to a target HGB concentration of 12 to 14 g/dL (SmPC Section 4.4). Epoetin alfa should be discontinued in non-responding patients (SmPC Section 4.2).	None
Survival impact	When used according to labelled guidance for correction of anaemia in the setting of CIA, there is no evidence that epoetin alfa has an adverse effect on survival. However, the data strongly suggest that epoetin alfa treatment increases the risk of death and serious cardiovascular events when administered to a target HGB concentration >12 g/dL (SmPC Sections 4.4 and 5.1); therefore, the target HGB concentration of 12 g/dL should not to be exceeded (SmPC Section 4.4). Patients should be monitored closely to ensure that the lowest approved dose of ESA is used to provide adequate control of symptoms of anaemia. Guidelines for dose and frequency of dose adjustments should be followed (SmPC Section 4.2)	None
Congestive heart failure	The target HGB should be up to 12 g/dL and should not be exceeded. Haemoglobin concentrations >12 g/dL may be associated with a higher risk of cardiovascular events in patients with CRF (SmPC Section 4.4).	None

CIA=chemotherapy-induced anaemia; CNS=central nervous system; CRF=chronic renal failure; ESA=erythropoiesis-stimulating agent; HGB=haemoglobin; IV=intravenous; PRCA=pure red cell aplasia; SmPC=Summary of Product Characteristics; TVE=thrombotic vascular event

VI.2. Elements for a Public Summary

EPREX belongs to a group of medicines called other antianemic preparations and is used to treat low red blood cell counts in patients. EPREX is available as a solution to be injected into a vein or under the skin.

VI.2.1. Overview of Disease Epidemiology

Red blood cells carry oxygen from the lungs to all parts of the body, giving it energy to function. EPREX increases red blood cell production in patients whose kidneys don't work properly, have low red blood cell counts from cancer treatments or bone marrow disease, donate their own blood before surgery, or are having hip or knee replacement surgery.

- Poor kidney function is common in patients more than 65 years old, but also occurs in younger adults and children, and is more common in women.
- Cancer treatments and bone marrow disease can hurt the body's ability to produce red blood cells. This is most comment in adult and older patients.
- The practice of donating one's own blood before surgery is limited in Europe and varies from country to country.
- Patients having hip or knee replacement surgery are generally more than 60 years old.

VI.2.2. Summary of Treatment Benefits

EPREX helps the body produce red blood cells and is given as an injection into a blood vessel or under the skin. The amount of drug, how often it's given, and how long it's used depend on the condition being treated and the patient's body weight, and are adjusted according to how well the treatment is working for the patient.

Drugs used to treat cancer and bone marrow disease can harm the body's ability to produce red blood cells. In these patients, EPREX has been shown to increase red blood cell amounts to normal levels.

Kidneys make an important hormone called erythropoietin that tells the body to make red blood cells. Kidneys that aren't working properly can't make enough erythropoietin, which causes the amount of red blood cells in the body to decrease. In patients with kidney problems, EPREX has been shown to increase red blood cell amounts to normal levels.

EPREX is used before surgery to increase red blood cell numbers and decrease the number of procedures needed to replace blood or portions of the blood lost during the surgical procedure.

EPREX has been effectively used in thousands of patients since it was first approved for use in 1988.

VI.2.3. Unknowns Relating to Treatment Benefits

Many patients of both sexes, and all races and ages have been treated with EPREX since the 1980s. Little information is available about the benefit of EPREX for anaemia associated with other diseases such as blood cancers as EPREX has not been studied in these conditions.

VI.2.4. Summary of Safety Concerns

Important Identified Risks

Risk	What is known	Preventability
Blood clots (thrombotic vascular events)	Blood clots may affect the patient's blood vessels, which may lead to painful swelling of the legs, and rarely, very dangerous clumping of blood cells in the lungs (blood clots). Clumped blood cells in the blood vessels near the heart may lead to a stroke.	Medicines to stop the clumping of blood cells may be prescribed by a doctor. Patients being treated with EPREX should be checked closely to make sure the lowest dose is used to adequately control the amount of protein in the blood that carries oxygen to all parts of the body (haemoglobin). Patients should receive medicine to help prevent blood cell clumping. EPREX should not be used in surgery patients who cannot receive medicines to prevent blood cell clumping. EPREX also should not be used in surgical patients in whom the amount of protein inside red blood cells that carry oxygen (haemoglobin) is above normal.
Reduced or stopped red blood cell production (pure red cell aplasia)	The reduction or absence of red blood cell production happens very rarely. It can stop EPREX from working and make the red blood cell count go even lower. EPREX should not be used in patients who develop this condition after being treated with any drug similar to EPREX.	EPREX should be given as an injection into a blood vessel according to the proper instructions.
High blood pressure (hypertension/hypertensive crisis)	High blood pressure is a common side effect of EPREX, but it can be treated. Blood pressure should be closely checked and controlled as needed, because if it is not treated, it can cause serious problems such as heart attacks and strokes.	High blood pressure can be managed by frequently checking blood pressure and giving medicine to lower blood pressure, as needed. EPREX should be used with caution in patients with poorly controlled high blood pressure and should not be used in patients with uncontrollable high blood pressure. If blood pressure cannot be controlled, EPREX treatment should be stopped.

Important Potential Risks

Risk	What is known
Worsening of disease (disease progression)	There is no evidence that EPREX may worsen a patient's cancer when used according to the Package Leaflet. However, if it is used differently, some patients with cancer who are treated with EPREX may be more likely to have their cancer worsen.
Increase in potential deaths (survival impact)	There is no evidence that EPREX may cause an increase in the possibility of death when used according to the Package Leaflet. However, if it is used differently, some patients with cancer treated with EPREX may be at a higher risk of dying.
Heart failure (congestive heart failure)	The protein in blood that carries oxygen (haemoglobin) must be maintained at the level stated in the Package Leaflet to lower the risk of heart failure in patients with kidneys that are not working properly.

Missing Information

Risk	What is known
None	Not applicable

VI.2.5 Summary of Additional Risk Minimisation Measures by Safety Concern

All medicines have an SmPC, which provides physicians, pharmacists, and other health care professionals with details on how to use the medicine, the safety risks, and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the Package Leaflet. The measures in these documents are known as routine risk minimisation measures.

The SmPC and Package Leaflet for EPREX are available nationally from the Company that makes EPREX.

The Company considers that the safety risks associated with this medicine can be managed with the information in the SmPC and Package Leaflet, and therefore no special conditions or restrictions for its safe and effective use (additional risk minimisation measures) have been proposed.

VI.2.6 Planned Postauthorisation Development Plan

List of Studies in Postauthorisation Development Plan

Study/activity (including study number)	Objectives	Safety concerns/ efficacy issue addressed	Status (planned, started)	Date for submission of (interim and) final results
Trial EPO-ANE-3010	Estimate how often patients treated drugs to fight breast cancer receiving EPREX plus red blood cell transfusions versus red blood cell transfusions alone developed worsening of their disease or blood clots	Worsening of disease; blood clots, increased risk of death	Ongoing	Report for final OS in 4Q 2017

OS=overall survival.

Studies Which are a Condition of the Marketing Authorisation

No trials are currently required as a condition of marketing authorisation.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
1.0	08 Dec 2004	Original version of RMP.	Submitted with response to EU Pharmacovigilance Working Party: Risk Management Plan for Potential Risk of Tumour Growth Progression in Cancer Patients Treated With Epoetins.
2.0	08 Jul 2005	Erythropoietin Ab-mediated PRCA in patients with CRF was added as an Important Identified Risk.	New risk identified.
3.0	24 Sep 2010	Information on 3 trials that have been completed: Trials EPO-AKD-3001, EPO-AKD-3002, EPO-ANE-4008, and EPO-CKD-2002.	Trial completion.
		Updated enrolment number for PRIMS.	
		Information on new ADR that will be added to the CCDS, but will not be added to the RMP.	Adverse drug reaction risks were identified but no new ones were considered as important for RMP purposes.
		Conclusion from Trial EPO-ANE-4008 on TVEs was added.	Trial completion.
		Update included number of cases of erythropoietin Ab-mediated PRCA in patients with CRF associated with EPREX in coated-stopper prefilled syringes containing PS-80 in countries where these cases originated.	
		Warning and precaution statement that was added to the product SmPC during this reporting interval for an unapproved patient population.	
4.0	26 Oct 2011	Exclusion Criteria were included in this section per the EMA template.	New template.
		Regulatory Actions Taken was updated to include worldwide actions taken due to safety issues.	Previously this was EU countries only.

Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
5.0		Updated document for consistency with template.	New template.
		Added proposed text for the MDS indication and updated other relevant sections of document with information from MDS studies.	New indication.
		Updated information on completed trials: EPOANE4076.	Trial completion.
5.1		Added new important potential risks: seizures and hypersensitivity/ anaphylaxis; updated important identified risk of "hypertension" to "hypertension/hypertensive crisis"	Updated document for consistency with the SmPC
5.2		Updated with data from CSR EPOANE3010 and additional subjects from the CSR EPOANE3021 extension. In addition, changed the frequency of immunogenicity reports from semiannual to annual.	Trial completion.
5.3		Risks of seizures and hypersensitivity/anaphylaxis were moved from important potential risks to important identified risks.	As requested by ANSM
5.4		Risks of seizures and hypersensitivity/anaphylaxis were removed	As requested by ANSM

Ab=antibody; ADR=adverse drug reaction; CCDS=Company Core Data Sheet; CRF=chronic renal failure; EMA=European Medicines Agency; EU=European Union; MDS=myelodysplastic syndrome; PRCA=pure red cell aplasia; PRIMS=Pharmacoepidemiology Registry EPO-ANE-4014 Prospective Immunogenicity Surveillance; PS-80=polysorbate-80; RMP=risk management plan; SmPC=Summary of Product Characteristics; TVE=thrombotic vascular event

SIGNATURES

Date	Justification
14Jun2018, 11:36:09 AM, UTC	Document Approval

LIST OF ANNEXES