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

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

| | | | |
|---|---|---|---|
| Data lock point for current RMP | 31 August 2018 | Version number | 6.0 |
| Date of final sign off | 25 March 2019 | Succession Number | 1 |
| | | | |

**Issue Date:** 25 March 2019
**Version Number:** 6.0, Succession 1
**Supersedes Version:** 5.4
**EDMS Number:** EDMS-ERI-173024372,1.4

QPPV Name(s): , PharmD, PhD

QPPV Signature: This RMP has been reviewed and approved by the MAH QPPV

| **Update to EU RMP** | |
|---|---|
| Version Number | 6.0, Succesion 1 |
| Rationale for submitting an updated RMP | This RMP was updated with the removal of Thrombotic vascular events and hypertension/hypertensive crisis as important identified risks and removal of congestive heart failure (CHF) as an important potential risk. These risks have been removed to align the safety concerns with the second revision of Good Pharmacovigilance Practices (GVP) Module V (rev 2).<br><br>In addition, this RMP update addresses the comments raised in the assessment report to align the current version with the outcome of procedure FR/H/003/09-10, 13-14/II/129 (approved RMP Version 5.4) and to modify the objectives of the annual immunogenicity reports.<br><br>RMP Version 5.2 was updated with data from CSR EPOANE3010 and additional subjects from the CSR EPOANE3021 extension. Study EPOANE3010 compared treatment with epoetin alfa plus standard supportive care with standard supportive care only in anaemic patients with metastatic breast cancer receiving standard chemotherapy. 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. To change the frequency of the immunogenicity reports from semi-annual to annual. |

| | |
|---|---|
| Summary of significant changes in the~~is~~ RMP | In this version of the RMP (Version 6.0, Succession 1), the following have been removed:<br><br>Important Identified Risks:<br><br>• Thrombotic vascular events<br>• Hypertension/hypertensive crisis<br><br>Important Potential Risks:<br>• Congestive heart failure<br><br>In addition, the draft wording to add Hypersensitivity/anaphylaxis and Seizures as important identified risks has been removed, in line with the outcome of procedure II/129.<br><br>Version 5.2 of the RMP has been updated to reflect the new template. The clinical exposure data has been updated with CSR EPOANE3010 and EPOANE3021 data. Additionally, the frequency of the immunogenicity reports has been changed from semiannual to annual. |

**Other RMP Versions Under Evaluation: None**

| RMP Version Number | Submitted on | Procedure Number |
|---|---|---|
| | | |

**Details of the Currently Approved RMP:**

| | |
|---|---|
| Version number of last agreed RMP: | What is the last approved version: 5.4 |
| Approved within procedure | EU MRP FR/H/003/09-10,13-14/II/129 |
| Date of approval (opinion date) | 28 June 2018 |

# TABLE OF CONTENTS

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

## Part I. - Product Overview

| | |
|---|---|
| **Active substance(s)**<br>**(INN or common name)** | Epoetin alfa |
| **Pharmacotherapeutic group(s) (ATC Code)** | Other antianemic preparations<br>B03XA01 |
| **Marketing Authorisation Holder** | Janssen-Cilag Pharma GmbH, Austria<br>Janssen-Cilag NV, Belgium<br>Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov, d.o.o., Bulgaria<br>Janssen-Cilag International NV, Cyprus<br>Janssen-Cilag s.r.o., Czech Republic<br>Janssen-Cilag A/S, Denmark<br>Janssen-Cilag OY, Finland<br>JANSSEN-CILAG, France<br>JANSSEN-CILAG GmbH, Germany<br>Janssen-Cilag Pharmaceutical S.A.C.I., Greece<br>Janssen-Cilag Limited, Ireland<br>Janssen-Cilag SpA, Italy<br>Janssen-Cilag, NV, Luxembourg<br>Janssen-Cilag International NV, Malta<br>Janssen-Cilag BV, Netherlands<br>Janssen-Cilag AS, Norway<br>Janssen-Cilag Farmaceutica, Lda, Portugal<br>Janssen-Cilag S.A., Romania<br>Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov d.o.o., Slovenia<br>Janssen-Cilag S.A., Spain<br>Janssen-Cilag AB, Sweden<br>Janssen-Cilag Ltd, United Kingdom |
| **Medicinal products to which the RMP refers** | 1 |
| **Invented name(s) in the European Economic Area (EEA)** | EPREX®/ERYPO® |
| **Marketing authorisation procedure** | Mutual recognition and National |

| | |
|---|---|
| **Brief description of the product** | Erythropoietin is a mitosis-stimulating factor and differentiating hormone, which stimulates erythropoiesis. |
| | 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. |
| | 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. |
| **Reference to the Product Information** | Mod.1.3.1 |
| **Indication(s) in the EEA**<br><br>**Current** | **<u>Chronic Renal Failure</u>**<br>EPREX, ERYPO is indicated for the treatment of symptomatic anaemia associated with chronic renal failure (CRF):<br>• In adults and paediatrics aged 1 to 18 years on haemodialysis and adult patients on peritoneal dialysis.<br>• In adults with renal insufficiency not yet undergoing dialysis for the treatment of severe anaemia of renal origin accompanied by clinical symptoms in patients.<br>**<u>Cancer</u>**<br>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.<br>**<u>Autologous Blood Donation</u>**<br>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**<br>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).<br><br>**Treatment of adult patients with low- or intermediate-1-risk myelodysplastic syndromes**<br>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) who have low serum erythropoietin (<200 mU/mL) |
| **Dosage in the EEA**<br>**Current** | **Treatment of symptomatic anaemia in adult chronic renal failure patients:**<br>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.<br>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.<br>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).<br>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.<br>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).<br>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.<br><br>Treatment with EPREX, ERYPO is divided into 2 stages – correction and maintenance phase.<br><br>**Adult haemodialysis patients**<br>In patients on haemodialysis where intravenous (IV) access is readily available, administration by the IV route is preferable.<br><br>**Correction phase:**<br><br>The starting dose is 50 international units (IU)/kg, 3 times per week.<br><br>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).<br><br>**Maintenance phase:**<br><br>The recommended total weekly dose is between 75 IU/kg and 300 IU/kg.<br><br>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).<br><br>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).<br><br>**Adult patients with renal insufficiency not yet undergoing dialysis**<br><br>Where IV access is not readily available EPREX, ERYPO may be administered subcutaneously.<br><br>**Correction phase:**<br><br>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).<br><br>**Maintenance phase:**<br><br>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.<br><br>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.<br><br>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.<br><br>**Adult peritoneal dialysis patients** |

| | |
|---|---|
| | Where IV access is not readily available, EPREX, ERYPO may be administered subcutaneously.<br><br>**Correction phase**:<br><br>The starting dose is 50 IU/kg, 2 times per week.<br><br>**Maintenance phase:**<br><br>The recommended maintenance dose is between 25 IU/kg and 50 IU/kg, 2 times per week in 2 equal injections.<br><br>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).<br><br>**Treatment of adult patients with chemotherapy-induced anaemia:**<br><br>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.<br><br>EPREX, ERYPO should be administered to patients with anaemia (eg, HGB concentration ≤10 g/dL [6.2 mmol/L]).<br><br>The initial dose is 150 IU/kg subcutaneously, 3 times per week.<br><br>Alternatively, EPREX, ERYPO can be administered at an initial dose of 450 IU/kg subcutaneously once weekly.<br><br>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).<br><br>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.<br><br>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).<br><br>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.<br><br>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.<br><br>**Dose adjustment to maintain HGB concentrations between 10 g/dL to 12 g/dL**<br><br>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%.<br><br>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.<br><br>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.<br><br>EPREX, ERYPO therapy should continue until 1 month after the end of chemotherapy.<br><br>**Treatment of adult surgery patients in an autologous blood donation programme:**<br><br>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.<br><br>**Treatment of adult patients scheduled for major elective orthopaedic surgery:**<br><br>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.<br><br>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.<br><br>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.<br><br>**Treatment of adult patients with low- or intermediate-1-risk MDS**<br><br>EPREX, ERYPO should be administered to patients with anaemia (eg, HGB concentration ≤10 g/dL [6.2 mmol/L]).<br><br>The recommended starting dose is EPREX, ERYPO 450 IU/kg (maximum total dose is 40,000 IU) administered subcutaneously once every week.<br><br>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).<br>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.<br>A sustained HGB concentration of greater than 12 g/dL (7.5 mmol/L) should be avoided.<br>EPREX, ERYPO should be administered as a SC injection. | | |
| **Pharmaceutical form(s) and strengths**<br>**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.<br>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. | | |
| Is/will 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.1: Epidemiology of the Indication(s) and Target Population(s)

## Indication(s)

### Chronic Renal Failure

*Adults*

**Incidence:**

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).

**Prevalence:**

A 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% (USRDS 2017).

**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 m2 body surface area (BSA) and 44% of patients with eGFR between 15 and 29 mL/min/1.73 m2 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*

**Incidence**

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)-National Institue for Health and Care Excellence (NICE) 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).

**Prevalence**

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 childaren (<19 years old) had prevalent ESRD, which represents a 1.3% decrease from the previous year (Saran 2015).

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 Population in the Authorised Indications - Age, Gender, Racial and/or Ethnic Origin] and Risk Factors for the Disease***

**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 it 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 2015).

In the United Kindgdom 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 (USRDS 2017). 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).

**The Main Existing 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).

**Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:**

**Adults**

Chronic kidney disease has a strong association with poor health outcomes and those at highest risk have an accelerated deterioration of kidney function, and significant albuminuria. They also have an increased risk of cardiovascular disease, (Stringer 2013). Symptoms of advanced CKD include chest pain, dry skin, feeling tired headaches, loss of appetite, muscle cramps, nausea/vomiting and weight loss. Anaemia commonly occurs in people with CKD. Anaemia might begin to develop in the early stages of CKD, when someone has 20 to 50% of normal kidney function, and the anaemia tends to worsen as CKD progresses. (NIDDK, 2014a)

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 2015).

**Children**

In children CKD tends to progress over time and eventually leads to kidney failure. Children with CKD tend to grow at a slower rate and urinary incontinence is common (NIDDK 2014b).

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 2015).

**Important Co-morbidities:**

***Chronic Renal Failure – Adult Patients***

Important co-morbidities in adult CRF patients include cardiovascular disease, hypertension, diabetes mellitus, hepatitis, cancer, and thrombosis.

***Chronic Renal Failure – Paediatric Patients***

Important co-morbidities in paediatric patients include hypertension, hepatitis, short stature, and thrombosis.

**Cancer**

**Incidence:**

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. Prevalance 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).

**Prevalence:**

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 Population in the Authorised Indication – Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Disease**

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).

**The Main Existing 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).

**Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity**

Anaemia in cancer patients can be associated with chemotherapy treatment due to the myelosuppressive effects of the treatment, and can also be associated with the disease itself. Anaemia can lead to fatigue and decreased quality of life in these patients, so management of this condition is important. (Aapro 2012) Also, anaemia in cancer patients has been linked to poorer outcomes and treatment response (Blohmer 2005).

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). Similary, 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).

**Important Co-morbidities:**

Co-morbidities in cancer patients can vary depending on cancer type and patient populations. More common co-morbidities include hypertension, cardiovascular disease and diabetes mellitus. The overall physical condition including depression and anxiety can severely affect cancer patients, and the severity of these conditions frequently impact the patient's outcome and survival.

**Autologous Blood Donation**

**Incidence:**

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

**Prevalence:**

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 US, ABD represented 4.0% of all blood donations (Goodnough 2004). In the US-for the years 2008-2011, of the more than 3,500,000 patients who underwent elective orthpaedic 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 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 Population in the Authorised Indication – Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Disease***

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 US, 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.

**The Main Existing Treatment Options:**

Not applicable

**Natural History of the Indicated Condition in the Untreated Population, Including 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).

**Important Co-morbidities:**

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

**Surgery**

**Incidence:**

**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).

**Prevalence:**

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 Population in the Authorised Indication – Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Disease***

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.

**The Main Existing Treatment Options:**

Not applicable

**Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity**

Surgery is a procedure and not a condition; therefore, there is no description of an untreated population.

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 examing 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).

**Important Co-morbidities:**

Important co-morbidities in surgery patients include obesity, osteoarthritits, cardiovascular disease, and hypertension.

**Myelodysplastic Syndromes**

**Incidence:**

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:**

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 of the Population in the Authorised Indication – Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Disease**

**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 ealier age in Asian populations (Fenaux 2014). However, another review from the United States noted that MDS was most prevaent 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 radition, and tobacco smoking. Reconized occupational factors include benzene and its deriviatives, while excess MDS cases have also been observed in agricultural and industrial workers.

**The Main Existing 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).

**Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity**

Most patients with MDS typically present with complications associated with peripheral blood cytopenias with approximately 50% present with anaemia. These conditions have a variable clinical course (Gangat, 2015). These syndromes are characterized by ineffective formation and development of blood cells, and they frequently progress to acute myeloid leukaemia, (AML), (Li 2013).

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).

**Important Co-morbidities:**

Important co-morbidities in patients with MDS include cardiovascular disease, diabetes, cerebrovascular diseases, and medical treatments for prior malignancies.

# PART II: SAFETY SPECIFICATION

## Module SII: Nonclinical Part of the Safety Specification

### 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. | 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).<br>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. |
| 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. | |

| Key Safety Findings (from nonclinical studies) | Relevance to Human Usage |
|---|---|
| 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. | |
| 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. |

| Key Safety Findings (from nonclinical studies) | Relevance to Human Usage |
|---|---|
| **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.<br><br>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.<br><br>Findings from repeated-dose toxicology studies in juvenile dogs and monkeys were consistent with those seen in adult animals. | 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. |
| **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.<br><br>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 assessed disease progression in anaemic patients with metastatic breast cancer receiving EPREX and chemotherapy. Refer to SVII.3 for additional details regarding Trial EPOANE-3010. |

| Key Safety Findings (from nonclinical studies) | Relevance to Human Usage |
|---|---|
| ***General safety pharmacology findings:*** | |
| **Cardiovascular (including potential for QT interval prolongation)** | |
| 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) | 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

### Conclusion of Nonclinical Safety Concerns

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.

| | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | None |

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

# PART II: SAFETY SPECIFICATION

## Module SIII: Clinical Trial Exposure

### SIII.1. Brief Overview of Development

*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 Indication*

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 EPOANE3018 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 14 March 2017 with the tables below summarising available patient-level data. This database includes 93 trials that enroled over 21,000 patients, of whom >70% (15,349 patients) were exposed to epoetin alfa.

### Exposure in Randomised Trials

The randomised trials population includes 69 trials listed below in which 7,595 patients were exposed to epoetin alfa.

- Trials in chronic renal failure – Dialysis: EP86-001 (CEO-C01), EP86-004 (2)
- Trials in chronic renal failure – Predialysis: EPO-AUS-14, EPO-CAN-10, EPO-ITA-7, EPOCKD2002, G86-011, H87-054 (6)
- Trials in oncology: 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, EPOANE3010

- Trials in ABD: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058
- Trials in surgery: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, PR97-19-002 (spine)
- Trials in MDS: EPOANE3018 and EPOANE3021

Exposure to EPREX in the randomised clinical trials population is summarised in Tables SIII.1 through SIII.4 for all subjects by duration, by age and gender, by dose, and variable stratifications relevant to the product (eg, renal impairment at baseline, hepatic impairment at baseline).

**Table SIII.1: Duration of Exposure: The Randomised Clinical Trials Population**

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

| INDICATION: All | | |
|---|---|---|
| Duration of Exposure | Patients (N=7595) | Person-months |
| < 1 month | 1827 | 1060.57 |
| 1 to < 3 months | 1946 | 4141.93 |
| 3 to < 6 months | 2154 | 9185.02 |
| 6 to < 9 months | 414 | 2873.03 |
| 9 to < 12 months | 283 | 3091.52 |
| 12 to < 18 months | 370 | 4995.75 |
| 18 to < 24 months | 201 | 4279.39 |
| 24 to < 36 months | 158 | 4533.39 |
| 36 to < 48 months | 102 | 4243.61 |
| 48 to < 60 months | 33 | 1780.99 |
| 60 to < 72 months | 22 | 1469.37 |
| 72 to < 84 months | 17 | 1297.87 |
| 84 to < 96 months | 12 | 1073.87 |
| 96 to < 108 months | 2 | 209.41 |
| 108 to < 120 months | 3 | 331.01 |
| 120 to < 132 months | 2 | 244.5 |
| Missing | 49 | . |
| Total person-months | 7595 | 44811.24 |

Note: 1 month equals to 365.25/12 days.
Chronic Renal Failure – Dialysis Studies: EP86-001 (CEO-C01), EP86-004
Chronic Renal Failure – Pre-dialysis 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, EPOANE3010
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: EPOANE3018 and EPOANE3021

[TSUB02.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub02.sas] 16JAN2018, 21:56

Exposure by Duration; All Randomised Controlled Clinical Trials

| INDICATION: Chronic Renal Failure – Dialysis | | |
|---|---|---|
| Duration of Exposure | Patients (N=97) | Person-months |
| < 1 month | 5 | 2.33 |
| 1 to < 3 months | 20 | 38.77 |
| 3 to < 6 months | 8 | 38.74 |
| 6 to < 9 months | 64 | 385.54 |
| Total person-months | 97 | 465.38 |

Note: 1 month equals to 365.25/12 days.
Chronic Renal Failure – Dialysis Studies: EP86-001 (CEO-C01), EP86-004

[TSUB01A.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub01a.sas] 16JAN2018, 21:56

Exposure by Duration; All Randomised Controlled Clinical Trials

| INDICATION: Chronic Renal Failure – Pre-dialysis | | |
|---|---|---|
| Duration of Exposure | Patients (N=464) | Person-months |
| < 1 month | 57 | 31.54 |
| 1 to < 3 months | 170 | 308.07 |
| 3 to < 6 months | 108 | 527.77 |
| 6 to < 9 months | 8 | 59.47 |
| 9 to < 12 months | 15 | 164.63 |
| 12 to < 18 months | 26 | 370.07 |
| 18 to < 24 months | 59 | 1352.02 |
| 24 to < 36 months | 16 | 390.24 |
| 36 to < 48 months | 4 | 182.14 |
| Missing | 1 | . |
| Total person-months | 464 | 3385.95 |

Note: 1 month equals to 365.25/12 days.
Chronic Renal Failure – Pre-dialysis Studies: EPO-AUS-14, EPO-CAN-10, EPO-ITA-7, EPOCKD2002, G86-011, H87-054.

[TSUB01B.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub01b.sas] 16JAN2018, 21:56

Exposure by Duration; All Randomised Controlled Clinical Trials

| INDICATION: Oncology | | |
|---|---|---|
| Duration of Exposure | Patients (N=5323) | Person-months |
| < 1 month | 337 | 186.51 |
| 1 to < 3 months | 1613 | 3577.63 |
| 3 to < 6 months | 1984 | 8353.12 |
| 6 to < 9 months | 334 | 2371.68 |
| 9 to < 12 months | 233 | 2546.6 |
| 12 to < 18 months | 344 | 4625.68 |
| 18 to < 24 months | 142 | 2927.38 |
| 24 to < 36 months | 142 | 4143.15 |
| 36 to < 48 months | 98 | 4061.47 |
| 48 to < 60 months | 33 | 1780.99 |
| 60 to < 72 months | 22 | 1469.37 |
| 72 to < 84 months | 17 | 1297.87 |
| 84 to < 96 months | 12 | 1073.87 |
| 96 to < 108 months | 2 | 209.41 |
| 108 to < 120 months | 3 | 331.01 |
| 120 to < 132 months | 2 | 244.5 |
| Missing | 5 | . |
| Total person-months | 5323 | 39200.23 |

Note: 1 month equals to 365.25/12 days.
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), EPOANE3010, EPO-CAN-29

[TSUB01C.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub01c.sas] 16JAN2018, 21:56

Exposure by Duration; All Randomised Controlled Clinical Trials

| INDICATION: Autologous Blood Donation | | |
|---|---|---|
| Duration of Exposure | Patients (N=402) | Person-months |
| < 1 month | 316 | 199.49 |
| 1 to < 3 months | 73 | 111.87 |
| 3 to < 6 months | 10 | 38.24 |
| 6 to < 9 months | 1 | 6.44 |
| Missing | 2 | . |
| Total person-months | 402 | 356.04 |

Note: 1 month equals to 365.25/12 days.
ABD Studies: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058

[TSUB01D.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub01d.sas] 16JAN2018, 21:56

Exposure by Duration; All Randomised Controlled Clinical Trials

| INDICATION: Surgery | | |
|---|---|---|
| Duration of Exposure | Patients (N=1207) | Person-months |
| < 1 month | 1106 | 638.32 |
| 1 to < 3 months | 58 | 80.43 |
| 3 to < 6 months | 2 | 7.29 |
| Missing | 41 | . |
| Total person-months | 1207 | 726.05 |

Note: 1 month equals to 365.25/12 days.
Surgery Studies: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, PR97-19-002 (spine).

[TSUB01E.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub01e.sas] 16JAN2018, 21:56

Exposure by Duration; All Randomised Controlled Clinical Trials

| INDICATION: MDS | | |
|---|---|---|
| Duration of Exposure | Patients (N=102) | Person-months |
| < 1 month | 6 | 2.37 |
| 1 to < 3 months | 12 | 25.17 |
| 3 to < 6 months | 42 | 219.86 |
| 6 to < 9 months | 7 | 49.91 |
| 9 to < 12 months | 35 | 380.29 |
| Total person-months | 102 | 677.59 |

Note: 1 month equals to 365.25/12 days.
MDS Studies: EPOANE3018 and EPOANE3021

[TSUB01G.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub01g.sas] 16JAN2018, 21:56

**Table SIII.2: Age Group and Gender: The Randomised Clinical Trials Population**

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

| | INDICATION: All | | | |
|---|---|---|---|---|
| | Men | | Women | |
| | Patients | Person-months | Patients | Person-months |
| Age Group | (N=2361) | | (N=5234) | |
| <18 years | 140 | 562.89 | 111 | 587.83 |
| 18 - 39 years | 130 | 543.51 | 521 | 4156.68 |
| 40 - 49 years | 229 | 747.53 | 996 | 8987.93 |
| 50 - 59 years | 470 | 1383.75 | 1416 | 12525.24 |
| 60 - 64 years | 370 | 1012.63 | 687 | 4856.97 |
| 65 - 69 years | 407 | 1132.58 | 540 | 2908.68 |
| 70 - 74 years | 322 | 1028.90 | 474 | 2062.92 |
| 75 - 79 years | 183 | 533.22 | 277 | 905.46 |
| 80 - 84 years | 70 | 191.18 | 128 | 306.33 |
| >=85 years | 39 | 120.97 | 84 | 256.03 |
| Missing | 1 | 0.00 | 0 | 0.00 |
| Total | 2361 | 7257.17 | 5234 | 37554.07 |

NOTE: Missing exposure data are not included in the calculation of person-months
Chronic Renal Failure – Dialysis Studies: EP86-001 (CEO-C01), EP86-004
Chronic Renal Failure – Pre-dialysis 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, EPOANE3010
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: EPOANE3018 and EPOANE3021

[TSUB06.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub06.sas] 16JAN2018, 21:57

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

| | INDICATION: Chronic Renal Failure – Dialysis | | | |
|---|---|---|---|---|
| | Men | | Women | |
| | Patients | Person-months | Patients | Person-months |
| Age Group | (N=57) | | (N=40) | |
| <18 years | 0 | 0.00 | 0 | 0.00 |
| 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 | 0.00 | 0 | 0.00 |
| >=85 years | 0 | 0.00 | 0 | 0.00 |
| Missing | 0 | 0.00 | 0 | 0.00 |
| Total | 57 | 280.7 | 40 | 184.6 |

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

[TSUB05A.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub05a.sas] 16JAN2018, 21:57

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

| | INDICATION: Chronic Renal Failure – Pre-dialysis | | | |
|---|---|---|---|---|
| | Men | | Women | |
| | Patients | Person-months | Patients | Person-months |
| Age Group | (N=226) | | (N=238) | |
| <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 |
| Total | 226 | 1625 | 238 | 1761 |

NOTE: Missing exposure data are not included in the calculation of person-months
Chronic Renal Failure – Pre-dialysis Studies: EPO-AUS-14, EPO-CAN-10, EPO-ITA-7, EPOCKD2002, G86-011, H87-054.

[TSUB05B.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub05b.sas] 16JAN2018, 21:57

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

| | INDICATION: Oncology | | | |
|---|---|---|---|---|
| | Men | | Women | |
| | Patients | Person-months | Patients | Person-months |
| Age Group | (N=1504) | | (N=3819) | |
| <18 years | 137 | 561.1 | 107 | 581.4 |
| 18 - 39 years | 36 | 122.3 | 403 | 3747 |
| 40 - 49 years | 135 | 390.8 | 852 | 8476 |
| 50 - 59 years | 315 | 952.0 | 1170 | 12161 |
| 60 - 64 years | 243 | 740.1 | 505 | 4414 |
| 65 - 69 years | 271 | 818.1 | 342 | 2620 |
| 70 - 74 years | 216 | 640.1 | 280 | 1772 |
| 75 - 79 years | 104 | 281.8 | 119 | 677.1 |
| 80 - 84 years | 35 | 99.02 | 30 | 103.7 |
| >=85 years | 12 | 19.22 | 11 | 23.85 |
| Missing | 0 | 0.00 | 0 | 0.00 |
| Total | 1504 | 4625 | 3819 | 34576 |

NOTE: 5 of the 5323 subjects are missing exposure data and are not included in the calculation of person-months
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), EPOANE3010, EPO-CAN-29

[TSUB05C.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub05c.sas] 16JAN2018, 21:57

Exposure by Age Group and Gender; All Randomised Controlled Trials

| | INDICATION: Autologous Blood Donation | | | |
|---|---|---|---|---|
| | Men | | Women | |
| | Patients | Person-months | Patients | Person-months |
| Age Group | (N=143) | | (N=259) | |
| <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 |
| Total | 143 | 137.1 | 259 | 218.9 |

NOTE: Missing exposure data are not included in the calculation of person-months
ABD Studies: 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\DBR_RMP_2018\RE_RMP_2018_EU\tsub05d.sas] 16JAN2018, 21:57

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

| | INDICATION: Surgery | | | |
|---|---|---|---|---|
| | Men | | Women | |
| | Patients | Person-months | Patients | Person-months |
| Age Group | (N=368) | | (N=839) | |
| <18 years | 0 | 0.00 | 0 | 0.00 |
| 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 |
| Total | 368 | 192.9 | 839 | 533.1 |

NOTE: Missing exposure data are not included in the calculation of person-months
Surgery Studies: 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\DBR_RMP_2018\RE_RMP_2018_EU\tsub05e.sas] 16JAN2018, 21:57

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

| | INDICATION: MDS | | | |
|---|---|---|---|---|
| | Men | | Women | |
| | Patients | Person-months | Patients | Person-months |
| Age Group | (N=63) | | (N=39) | |
| <18 years | 0 | 0.00 | 0 | 0.00 |
| 18 - 39 years | 0 | 0.00 | 0 | 0.00 |
| 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 |
| Total | 63 | 396.52 | 39 | 281.07 |

MDS Studies: EPOANE3018 and EPOANE3021

[TSUB05G.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub05g.sas] 16JAN2018, 21:57

**Table SIII.3: Exposure by Dose: The Randomised Clinical Trials Population**

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

| INDICATION: All | | |
|---|---|---|
| Initial dose level | Patients(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 | 30110.52 |
| 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 | 44811.24 |

NOTE: Missing exposure data are not included in the calculation of person-months
Chronic Renal Failure – Dialysis Studies: EP86-001 (CEO-C01), EP86-004
Chronic Renal Failure – Pre-dialysis 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, EPOANE3010
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: EPOANE3018 and EPOANE3021

[TSUB04.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub04.sas] 16JAN2018, 21:57

Exposure by Dose; All Randomised Controlled Clinical Trials

| INDICATION: Chronic Renal Failure – Dialysis | | |
|---|---|---|
| Initial dose level | Patients(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 |

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

[TSUB03A.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub03a.sas] 16JAN2018, 21:56

Exposure by Dose; All Randomised Controlled Clinical Trials

| INDICATION: Chronic Renal Failure – Pre-dialysis | | |
|---|---|---|
| Initial dose level | Patients(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 |

NOTE: Missing exposure data are not included in the calculation of person-months
Chronic Renal Failure – Pre-dialysis Studies: EPO-AUS-14, EPO-CAN-10, EPO-ITA-7, EPOCKD2002, G86-011, H87-054.

[TSUB03B.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub03b.sas] 16JAN2018, 21:56

Exposure by Dose; All Randomised Controlled Clinical Trials

| INDICATION: Oncology | | |
|---|---|---|
| Initial dose level | Patients(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 | 29927.46 |
| 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 | 39200.23 |

NOTE: Missing exposure data are not included in the calculation of person-months
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), EPOANE3010, EPO-CAN-29

[TSUB03C.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub03c.sas] 16JAN2018, 21:56

Exposure by Dose; All Randomised Controlled Clinical Trials

| INDICATION: Autologous Blood Donation | | |
|---|---|---|
| Initial dose level | Patients(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 |

NOTE: Missing exposure data are not included in the calculation of person-months
ABD Studies: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058

[TSUB03D.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub03d.sas] 16JAN2018, 21:56

Exposure by Dose; All Randomised Controlled Clinical Trials

| INDICATION: Surgery | | |
|---|---|---|
| Initial dose level | Patients(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 |

NOTE: Missing exposure data are not included in the calculation of person-months
Surgery Studies: 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\DBR_RMP_2018\RE_RMP_2018_EU\tsub03e.sas] 16JAN2018, 21:57

Exposure by Dose; All Randomised Controlled Clinical Trials

| INDICATION: MDS | | |
|---|---|---|
| Initial dose level | Patients(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 Studies: EPOANE3018 and EPOANE3021

[TSUB03G.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub03g.sas] 16JAN2018, 21:57

**Table SIII.4: Exposure by Special Populations: The Randomised Clinical Trials Population (eg, Renal Impairment at Baseline, Hepatic Impairment at Baseline)**

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

| INDICATION: All | | | |
|---|---|---|---|
| Population | Category at Baseline | Patients | Person-months |
| Total | | (N=7595) | |
| Hepatic Impairment[a] | | (n=4949) | |
| ALT | | | |
| | <=ULN (normal) | 3871 | 29490.20 |
| | >ULN to <=2.5 x ULN | 590 | 5810.14 |
| | >2.5 to <=5.0 x ULN | 83 | 665.13 |
| | >5.0 to <=20.0 x ULN | 35 | 210.46 |
| | >20.0 x ULN | 10 | 46.29 |
| | Missing | 360 | |
| AST | | | |
| | <=ULN (normal) | 3989 | 27919.64 |
| | >ULN to <=2.5 x ULN | 743 | 7502.78 |
| | >2.5 to <=5.0 x ULN | 86 | 678.67 |
| | >5.0 to <=20.0 x ULN | 31 | 172.81 |
| | >20.0 x ULN | 8 | 32.23 |
| | Missing | 92 | |
| Bilirubin | | | |
| | <=ULN (normal) | 4258 | 33436.65 |
| | >ULN to <=1.5 x ULN | 133 | 1608.18 |
| | >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) | 3382 | 24688.79 |
| | >ULN to <=2.5 x ULN | 1066 | 9439.41 |
| | >2.5 to <=5.0 x ULN | 188 | 1751.79 |
| | >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 | 13097.76 |
| | Moderate (CrCl>30 to <=50 mL/min) | 565 | 2380.68 |
| | Severe (CrCl<=30 mL/min) | 60 | 148.99 |
| | Missing or Other[b] | 2385 | |

Person-months may be underestimated due to missing exposure data.
[a] Of 7595 subjects, 4949 had data measuring hepatic impairment. For each parameter measured, some subjects did not have data available and are counted as missing.
For Renal Impairment, only studies associated with Oncology, ABD and Surgery indications are included
[b] Of the 4920 subjects with CrCl data, only 2535 were categorized as mild, moderate or severe with respect to renal impairment. The remaining 2385 subjects were normal or missing baseline CrCl.
Chronic Renal Failure – Dialysis Studies: EP86-001 (CEO-C01), EP86-004
Chronic Renal Failure – Pre-dialysis 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, EPOANE3010
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: EPOANE3018 and EPOANE3021

[TSUB010.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub010.sas] 16JAN2018, 21:58

Exposure by Special Population; All Randomised Controlled Clinical Trials

INDICATION: Chronic Renal Failure – Dialysis

| Population | Category at Baseline | Patients | 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 | |

Of 97 subjects in the Chronic Renal Failure – Adult Haemodialysis dataset, 97 had data at least one non-missing hepatic ALT, AST, BILIRUBIN or alkaline phosphatase measurement. For each parameter measured, some of the 97 subjects did not have data available and are counted as missing.
Chronic Renal Failure – Dialysis Studies: EP86-001 (CEO-C01), EP86-004

[TSUB09A.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub09a.sas] 16JAN2018, 21:57

Exposure by Special Population; All Randomised Controlled Clinical Trials

INDICATION: Chronic Renal Failure – Pre-dialysis

| Population | Category at Baseline | Patients | 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* | |

Person-months may be underestimated due to missing exposure data.
Of 464 subjects in the Chronic Renal Failure – Adult Pre-dialysis dataset, 395 had data at least one non-missing hepatic ALT, AST, BILIRUBIN or alkaline phosphatase measurement. For each parameter measured, some of the 395 subjects did not have data available and are counted as missing.
Chronic Renal Failure – Pre-dialysis Studies: EPO-AUS-14, EPO-CAN-10, EPO-ITA-7, EPOCKD2002, G86-011, H87-054.

[TSUB09B.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub09b.sas] 16JAN2018, 21:57

Exposure by Special Population; All Randomised Controlled Clinical Trials

| INDICATION: Oncology | | | |
|---|---|---|---|
| Population | Category at Baseline | Patients | Person-months |
| Total | | (N=5323) | |
| Hepatic Impairment[a] | | (n=3130) | |
| ALT | | | |
| | <=ULN (normal) | 2442 | 25162.55 |
| | >ULN to <=2.5 x ULN | 482 | 5561.63 |
| | >2.5 to <=5.0 x ULN | 74 | 634.78 |
| | >5.0 to <=20.0 x ULN | 31 | 198.14 |
| | >20.0 x ULN | 10 | 46.29 |
| | Missing | 91 | |
| AST | | | |
| | <=ULN (normal) | 2334 | 23709.21 |
| | >ULN to <=2.5 x ULN | 636 | 7296.62 |
| | >2.5 to <=5.0 x ULN | 77 | 628.86 |
| | >5.0 to <=20.0 x ULN | 31 | 172.81 |
| | >20.0 x ULN | 8 | 32.23 |
| | Missing | 44 | |
| Bilirubin | | | |
| | <=ULN (normal) | 2719 | 29177.89 |
| | >ULN to <=1.5 x ULN | 109 | 1586.76 |
| | >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) | 1871 | 20763.10 |
| | >ULN to <=2.5 x ULN | 785 | 8469.39 |
| | >2.5 to <=5.0 x ULN | 182 | 1714.07 |
| | >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 | 12719.93 |
| | Moderate (CrCl>30 to <=50 mL/min) | 339 | 2235.27 |
| | Severe (CrCl<=30 mL/min) | 43 | 139.14 |
| | Missing or Other[b] | 1648 | |

Person-months may be underestimated due to missing exposure data.
[a] Of 5323 subjects in the Oncology dataset, 3130 had data measuring hepatic impairment. For each parameter measured, some subjects did not have data available and are counted as missing.
[b] Of the 3372 subjects with CrCl data, only 1724 were categorized as mild, moderate or severe with respect to renal impairment. The remaining 1648 subjects 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), EPOANE3010, EPO-CAN-29

[TSUB09C.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub09c.sas] 16JAN2018, 21:57

Exposure by Special Population; All Randomised Controlled Clinical Trials

| INDICATION: Autologous Blood Donation | | | |
|---|---|---|---|
| Population | Category at Baseline | Patients | 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 | |

Person-months may be underestimated due to missing exposure data.
[a] Of 402 subjects in the ABD dataset, 398 had data measuring hepatic impairment. For each parameter measured, some subjects did not have data available and are counted as missing.
[b] Of the 390 subjects with CrCl data, only 186 were categorized as mild, moderate or severe with respect to renal impairment. The remaining 204 subjects were normal or missing baseline CrCl.
ABD Studies: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058

[TSUB09D.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub09d.sas] 16JAN2018, 21:57

Exposure by Special Population; All Randomised Controlled Clinical Trials

| INDICATION: Surgery | | | |
|---|---|---|---|
| Population | Category at Baseline | Patients | 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 | |

Person-months may be underestimated due to missing exposure data.
[a] Of 1207 subjects in the Surgery dataset, 830 had data measuring hepatic impairment. For each parameter measured, some subjects did not have data available and are counted as missing.
[b] Of the 1158 subjects with CrCl data, only 625 were categorized as mild, moderate or severe with respect to renal impairment. The remaining 533 subjects were normal or missing baseline CrCl.
Surgery Studies: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, PR97-19-002 (spine)

[TSUB09E.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub09e.sas] 16JAN2018, 21:57

Exposure by Special Population; All Randomised Controlled Clinical Trials

| INDICATION: MDS | | | |
|---|---|---|---|
| Population | Category at Baseline | Patients | 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 | |

Of 102 subjects in the MDS dataset, 99 had data at least one non-missing hepatic ALT, AST, BILIRUBIN or alkaline phosphatase measurement. For each parameter measured, some of the 99 subjects did not have data available and are counted as missing.
MDS Studies: EPOANE3018 and EPOANE3021

[TSUB09G.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub09g.sas] 16JAN2018, 21:57

**Exposure in All Clinical Trials**

The all clinical trials population includes 93 trials listed below in which 15,349 patients were exposed to epoetin alfa.

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 – Pre-dialysis 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, EPOANE4008, 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, EPOANE3010

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: EPOANE3018 and EPOANE3021

Exposure to EPREX in the all clinical trials population is summarised in Tables SIII.5 through SIII.8 for all subjects by duration, by age and gender, by dose, and variable stratifications relevant to the product (eg, renal impairment at baseline, hepatic impairment at baseline).

**Table SIII.5: Duration of Exposure: All Clinical Trials Populations**

Exposure by Duration (Totals); All Clinical Trials Including Open Extension

INDICATION: All

| Duration of Exposure | Patients (N=15349) | Person-months |
|---|---|---|
| < 1 month | 2363 | 1342.32 |
| 1 to < 3 months | 3039 | 6394.32 |
| 3 to < 6 months | 4941 | 20003.32 |
| 6 to < 9 months | 1313 | 9633.51 |
| 9 to < 12 months | 860 | 9053.17 |
| 12 to < 18 months | 1228 | 17856.94 |
| 18 to < 24 months | 962 | 20444.93 |
| 24 to < 36 months | 365 | 10596.96 |
| 36 to < 48 months | 104 | 4321.05 |
| 48 to < 60 months | 33 | 1780.99 |
| 60 to < 72 months | 22 | 1469.37 |
| 72 to < 84 months | 17 | 1297.87 |
| 84 to < 96 months | 12 | 1073.87 |
| 96 to < 108 months | 2 | 209.41 |
| 108 to < 120 months | 3 | 331.01 |
| 120 to < 132 months | 2 | 244.5 |
| Missing | 83 | . |
| Total person-months | 15349 | 106053.56 |

Note: 1 month equals to 365.25/12 days.
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 – Pre-dialysis 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, EPOANE4008, 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, EPOANE3010
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: EPOANE3018 and EPOANE3021

[TSUB012.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub012.sas] 16JAN2018, 21:58

Exposure by Duration; All Clinical Trials Including Open Extension

INDICATION: Chronic Renal Failure – Dialysis

| Duration of Exposure | Patients (N=2046) | Person-months |
|---|---|---|
| < 1 month | 81 | 44.32 |
| 1 to < 3 months | 306 | 611.12 |
| 3 to < 6 months | 510 | 2245.09 |
| 6 to < 9 months | 384 | 2601.56 |
| 9 to < 12 months | 128 | 1325.9 |
| 12 to < 18 months | 241 | 3724.39 |
| 18 to < 24 months | 363 | 7953.84 |
| Missing | 33 | . |
| Total person-months | 2046 | 18506.22 |

Note: 1 month equals to 365.25/12 days.
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)

[TSUB011A.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub011a.sas] 16JAN2018, 21:58

Exposure by Duration; All Clinical Trials Including Open Extension

INDICATION: Chronic Renal Failure – Pre-dialysis

| Duration of Exposure | Patients (N=5610) | Person-months |
|---|---|---|
| < 1 month | 328 | 159.77 |
| 1 to < 3 months | 793 | 1619.12 |
| 3 to < 6 months | 2115 | 7873.97 |
| 6 to < 9 months | 579 | 4551.95 |
| 9 to < 12 months | 479 | 4964.9 |
| 12 to < 18 months | 630 | 9290.48 |
| 18 to < 24 months | 456 | 9540.21 |
| 24 to < 36 months | 222 | 6429.11 |
| 36 to < 48 months | 6 | 259.58 |
| Missing | 2 | . |
| Total person-months | 5610 | 44689.08 |

Note: 1 month equals to 365.25/12 days.
Chronic Renal Failure – Pre-dialysis 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

[TSUB011B.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub011b.sas] 16JAN2018, 21:58

Exposure by Duration; All Clinical Trials Including Open Extension

| INDICATION: Oncology | | |
|---|---|---|
| Duration of Exposure | Patients (N=5827) | Person-months |
| < 1 month | 380 | 210.66 |
| 1 to < 3 months | 1797 | 3946.61 |
| 3 to < 6 months | 2255 | 9584.76 |
| 6 to < 9 months | 340 | 2408.67 |
| 9 to < 12 months | 233 | 2546.6 |
| 12 to < 18 months | 344 | 4625.68 |
| 18 to < 24 months | 142 | 2927.38 |
| 24 to < 36 months | 142 | 4143.15 |
| 36 to < 48 months | 98 | 4061.47 |
| 48 to < 60 months | 33 | 1780.99 |
| 60 to < 72 months | 22 | 1469.37 |
| 72 to < 84 months | 17 | 1297.87 |
| 84 to < 96 months | 12 | 1073.87 |
| 96 to < 108 months | 2 | 209.41 |
| 108 to < 120 months | 3 | 331.01 |
| 120 to < 132 months | 2 | 244.5 |
| Missing | 5 | . |
| Total person-months | 5827 | 40862 |

Note: 1 month equals to 365.25/12 days.
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, EPOANE4008, 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), EPOANE3010, EPO-CAN-29

[TSUB011C.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub011c.sas] 16JAN2018, 21:58

Exposure by Duration; All Clinical Trials Including Open Extension

| INDICATION: Autologous Blood Donation | | |
|---|---|---|
| Duration of Exposure | Patients (N=402) | Person-months |
| < 1 month | 316 | 199.49 |
| 1 to < 3 months | 73 | 111.87 |
| 3 to < 6 months | 10 | 38.24 |
| 6 to < 9 months | 1 | 6.44 |
| Missing | 2 | . |
| Total person-months | 402 | 356.04 |

Note: 1 month equals to 365.25/12 days.
ABD Studies: 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\DBR_RMP_2018\RE_RMP_2018_EU\tsub011d.sas] 16JAN2018, 21:58

Exposure by Duration; All Clinical Trials Including Open Extension

| INDICATION: Surgery | | |
|---|---|---|
| Duration of Exposure | Patients (N=1352) | Person-months |
| < 1 month | 1251 | 725.06 |
| 1 to < 3 months | 58 | 80.43 |
| 3 to < 6 months | 2 | 7.29 |
| Missing | 41 | . |
| Total person-months | 1352 | 812.78 |

Note: 1 month equals to 365.25/12 days.
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)

[TSUB011E.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub011e.sas] 16JAN2018, 21:58

Exposure by Duration; All Clinical Trials Including Open Extension

| INDICATION: MDS | | |
|---|---|---|
| Duration of Exposure | Patients (N=112) | Person-months |
| < 1 month | 7 | 3.02 |
| 1 to < 3 months | 12 | 25.17 |
| 3 to < 6 months | 49 | 253.96 |
| 6 to < 9 months | 9 | 64.89 |
| 9 to < 12 months | 20 | 215.79 |
| 12 to < 18 months | 13 | 216.51 |
| 18 to < 24 months | 1 | 23.52 |
| 24 to < 36 months | 1 | 24.71 |
| Total person-months | 112 | 827.57 |

Note: 1 month equals to 365.25/12 days.
Note: 10 subjects who switched from PBO to EPO during the OLE are added to the EPO exposure for the duration accordingly during which they are exposed to EPO.

[TSUB011G.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub011g.sas] 16JAN2018, 21:58

**Table SIII.6: Age and Gender: All Clinical Trials Populations**

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

| | INDICATION: All | | | |
|---|---|---|---|---|
| | Men | | Women | |
| | Patients | Person-months | Patients | Person-months |
| Age Group | (N=5913) | | (N=9436) | |
| <18 years | 142 | 567.10 | 114 | 599.95 |
| 18 - 39 years | 485 | 3669.78 | 915 | 7052.16 |
| 40 - 49 years | 592 | 3965.40 | 1440 | 12358.18 |
| 50 - 59 years | 1083 | 6521.07 | 2195 | 18306.76 |
| 60 - 64 years | 788 | 4384.43 | 1196 | 8919.17 |
| 65 - 69 years | 878 | 4783.97 | 1089 | 7462.24 |
| 70 - 74 years | 820 | 5146.94 | 1041 | 6315.99 |
| 75 - 79 years | 593 | 3854.98 | 726 | 4254.06 |
| 80 - 84 years | 313 | 1979.50 | 439 | 2794.09 |
| >=85 years | 216 | 1454.26 | 279 | 1656.65 |
| Missing | 3 | 3.06 | 2 | 3.98 |
| Total | 5913 | 36330.48 | 9436 | 69723.21 |

NOTE: Missing exposure data are not included in the calculation of person-months
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 – Pre-dialysis 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, EPOANE4008, 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, EPOANE3010
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: EPOANE3018 and EPOANE3021

[TSUB016.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub016.sas] 16JAN2018, 21:59

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

| | INDICATION: Chronic Renal Failure – Dialysis | | | |
|---|---|---|---|---|
| | Men | | Women | |
| | Patients | Person-months | Patients | Person-months |
| Age Group | (N=1149) | | (N=897) | |
| <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 |
| Total | 1149 | 10785 | 897 | 7721 |

NOTE: Missing exposure data are not included in the calculation of person-months.
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)

[TSUB015A.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub015a.sas] 16JAN2018, 21:58

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

| | INDICATION: Chronic Renal Failure – Pre-dialysis | | | |
|---|---|---|---|---|
| | Men | | Women | |
| | Patients | Person-months | Patients | Person-months |
| Age Group | (N=2503) | | (N=3107) | |
| <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 |
| Total | 2503 | 19578 | 3107 | 25111 |

NOTE: Missing exposure data are not included in the calculation of person-months.
Chronic Renal Failure – Pre-dialysis 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

[TSUB015B.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub015b.sas] 16JAN2018, 21:58

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

| | INDICATION: Oncology | | | |
|---|---|---|---|---|
| | Men | | Women | |
| | Patients | Person-months | Patients | Person-months |
| Age Group | (N=1671) | | (N=4156) | |
| <18 years | 137 | 561.1 | 107 | 581.4 |
| 18 - 39 years | 48 | 162.7 | 438 | 3858 |
| 40 - 49 years | 146 | 423.5 | 916 | 8672 |
| 50 - 59 years | 352 | 1066 | 1266 | 12482 |
| 60 - 64 years | 271 | 823.4 | 557 | 4597 |
| 65 - 69 years | 302 | 935.8 | 382 | 2777 |
| 70 - 74 years | 239 | 720.8 | 308 | 1855 |
| 75 - 79 years | 120 | 320.9 | 132 | 721.3 |
| 80 - 84 years | 41 | 116.2 | 37 | 132.4 |
| >=85 years | 15 | 26.38 | 13 | 29.37 |
| Missing | 0 | 0.00 | 0 | 0.00 |
| Total | 1671 | 5157 | 4156 | 35705 |

NOTE: Missing exposure data are not included in the calculation of person-months.
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, EPOANE4008, 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), EPOANE3010, EPO-CAN-29

[TSUB015C.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub015c.sas] 16JAN2018, 21:58

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

| | INDICATION: Autologous Blood Donation | | | |
|---|---|---|---|---|
| | Men | | Women | |
| | Patients | Person-months | Patients | Person-months |
| Age Group | (N=143) | | (N=259) | |
| <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 |
| Total | 143 | 137.1 | 259 | 218.9 |

NOTE: Missing exposure data are not included in the calculation of person-months
ABD Studies: 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\DBR_RMP_2018\RE_RMP_2018_EU\tsub015d.sas] 16JAN2018, 21:59

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

| | INDICATION: MDS | | | |
|---|---|---|---|---|
| | Men | | Women | |
| | Patients | Person-months | Patients | Person-months |
| Age Group | (N=69) | | (N=43) | |
| <18 years | 0 | 0.00 | 0 | 0.00 |
| 18 - 39 years | 0 | 0.00 | 0 | 0.00 |
| 40 - 49 years | 1 | 1.64 | 1 | 5.49 |
| 50 - 59 years | 3 | 10.48 | 2 | 16.39 |
| 60 - 64 years | 4 | 25.56 | 3 | 35.75 |
| 65 - 69 years | 8 | 65.97 | 4 | 22.77 |
| 70 - 74 years | 17 | 120.41 | 13 | 82.23 |
| 75 - 79 years | 18 | 122.68 | 7 | 59.86 |
| 80 - 84 years | 9 | 73.56 | 9 | 88.18 |
| >=85 years | 9 | 54.57 | 4 | 42.02 |
| Missing | 0 | 0.00 | 0 | 0.00 |
| Total | 69 | 474.88 | 43 | 352.69 |

MDS Studies: EPOANE3018 and EPOANE3021
Note: 10 subjects who switched from PBO to EPO during the OLE are added to the EPO exposure for the duration accordingly during which they are exposed to EPO.

[TSUB015G.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub015g.sas] 16JAN2018, 21:59

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

| | INDICATION: Surgery | | | |
|---|---|---|---|---|
| | Men | | Women | |
| | Patients | Person-months | Patients | Person-months |
| Age Group | (N=378) | | (N=974) | |
| <18 years | 0 | 0.00 | 0 | 0.00 |
| 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 |
| Total | 378 | 198.8 | 974 | 613.9 |

NOTE: Missing exposure data are not included in the calculation of person-months.
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)

[TSUB015E.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub015e.sas] 16JAN2018, 21:59

**Table SIII.7: Exposure by Dose: All Clinical Trials Populations**

**Cumulative for all Indications**

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

| INDICATION: All | | |
|---|---|---|
| Initial dose level | Patients(N=15349) | 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 | 337 | 1577.17 |
| 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 | 30110.52 |
| 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 | 15349 | 106053.56 |

NOTE: Missing exposure data are not included in the calculation of person-months
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 – Pre-dialysis 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, EPOANE4008, 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, EPOANE3010
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: EPOANE3018 and EPOANE3021

[TSUB014.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub014.sas] 16JAN2018, 21:58

Exposure by Dose; All Clinical Trials Including Open Extension

| INDICATION: Chronic Renal Failure – Dialysis | | |
|---|---|---|
| Initial dose level | Patients(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 |

NOTE: Missing exposure data are not included in the calculation of person-months
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)

[TSUB013A.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub013a.sas] 16JAN2018, 21:58

Exposure by Dose; All Clinical Trials Including Open Extension

| INDICATION: Chronic Renal Failure – Pre-dialysis | | |
|---|---|---|
| Initial dose level | Patients(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 |

NOTE: Missing exposure data are not included in the calculation of person-months
Chronic Renal Failure – Pre-dialysis 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

[TSUB013B.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub013b.sas] 16JAN2018, 21:58

Exposure by Dose; All Clinical Trials Including Open Extension

| INDICATION: Oncology | | |
|---|---|---|
| Initial dose level | Patients(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 | 29927.46 |
| 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 | 40862 |

NOTE: Missing exposure data are not included in the calculation of person-months
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, EPOANE4008, 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), EPOANE3010, EPO-CAN-29

[TSUB013C.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub013c.sas] 16JAN2018, 21:58

Exposure by Dose; All Clinical Trials Including Open Extension

| INDICATION: Autologous Blood Donation | | |
|---|---|---|
| Initial dose level | Patients(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 |

NOTE: Missing exposure data are not included in the calculation of person-months
ABD Studies: 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\DBR_RMP_2018\RE_RMP_2018_EU\tsub013d.sas] 16JAN2018, 21:58

Exposure by Dose; All Clinical Trials Including Open Extension

| INDICATION: Surgery | | |
|---|---|---|
| Initial dose level | Patients(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 |

NOTE: Missing exposure data are not included in the calculation of person-months
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)

[TSUB013E.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub013e.sas] 16JAN2018, 21:58

Exposure by Dose; All Clinical Trials Including Open Extension

| INDICATION: MDS | | |
|---|---|---|
| Initial dose level | Patients(N=112) | Person-months |
| 450 IU/kg QW | 95 | 753.68 |
| 40,000 IU QW | 8 | 23.39 |
| 80,000 IU QW | 9 | 50.5 |
| Total | 112 | 827.57 |

MDS Studies: EPOANE3018 and EPOANE3021
Note: 10 subjects who switched from PBO to EPO during the OLE are added to the EPO exposure for the duration accordingly during which they are exposed to EPO.

[TSUB013G.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub013g.sas] 16JAN2018, 21:58

**Table SIII.8: Exposure by Special Populations: All Clinical Trials Populations (eg, Renal Impairment at Baseline, Hepatic Impairment at Baseline)**

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

| INDICATION: All | | | |
|---|---|---|---|
| Population | Category at Baseline | Patients | Person-months |
| Total | | (N=15349) | |
| Hepatic Impairment[a] | | (n=9679) | |
| ALT | | | |
| | <=ULN (normal) | 8252 | 75478.60 |
| | >ULN to <=2.5 x ULN | 751 | 7411.45 |
| | >2.5 to <=5.0 x ULN | 94 | 780.81 |
| | >5.0 to <=20.0 x ULN | 36 | 231.89 |
| | >20.0 x ULN | 10 | 46.29 |
| | Missing | 536 | |
| AST | | | |
| | <=ULN (normal) | 8315 | 73392.99 |
| | >ULN to <=2.5 x ULN | 942 | 9422.72 |
| | >2.5 to <=5.0 x ULN | 95 | 766.52 |
| | >5.0 to <=20.0 x ULN | 32 | 173.31 |
| | >20.0 x ULN | 8 | 32.23 |
| | Missing | 287 | |
| Bilirubin | | | |
| | <=ULN (normal) | 8766 | 80931.02 |
| | >ULN to <=1.5 x ULN | 152 | 1712.53 |
| | >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 | 493 | |
| Alkaline phosphatase | | | |
| | <=ULN (normal) | 6729 | 57177.19 |
| | >ULN to <=2.5 x ULN | 1610 | 14479.24 |
| | >2.5 to <=5.0 x ULN | 218 | 1930.35 |
| | >5.0 to <=20.0 x ULN | 61 | 443.27 |
| | >20.0 x ULN | 9 | 39.16 |
| | Missing | 1052 | |
| Renal impairment | | (n=5544) | |
| | Mild (CrCl>50 to <80 mL/min) | 2183 | 14046.33 |
| | Moderate (CrCl>30 to <=50 mL/min) | 659 | 2741.61 |
| | Severe (CrCl<=30 mL/min) | 73 | 209.51 |
| | Missing or Other[b] | 2629 | |

Person-months may be underestimated due to missing exposure data.
[a] Of 15349 subjects, 9679 had data measuring hepatic impairment. For each parameter measured, some subjects did not have data available and are counted as missing.
For Renal Impairment, only studies associated with Oncology, ABD, Surgery and MDS indications are included.
[b] Of the 5544 subjects with CrCl data, only 2915 were categorized as mild, moderate or severe with respect to renal impairment. The remaining 2629 subjects 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 – Pre-dialysis 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, EPOANE4008, 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, EPOANE3010
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: EPOANE3018 and EPOANE3021

[TSUB020.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub020.sas] 16JAN2018, 21:59

Exposure by Special Population; All Clinical Trials Including Open Extension

| INDICATION: Chronic Renal Failure – Dialysis | | | |
|---|---|---|---|
| Population | Category at Baseline | Patients | 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 | |

Person-months may be underestimated due to missing exposure data.
Of 2046 subjects in the Chronic Renal Failure – Adult Haemodialysis dataset, 907 had data at least one non-missing hepatic ALT, AST, BILIRUBIN or alkaline phosphatase measurement. For each parameter measured, some of the 907 subjects did not have data available and are counted as missing.
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)

[TSUB019A.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub019a.sas] 16JAN2018, 21:59

Exposure by Special Population; All Clinical Trials Including Open Extension

| INDICATION: Chronic Renal Failure – Pre-dialysis | | | |
|---|---|---|---|
| Population | Category at Baseline | Patients | 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 | |

Person-months may be underestimated due to missing exposure data.
Of 5610 subjects in the Chronic Renal Failure – Adult Pre-dialysis dataset, 3796 had data at least one non-missing hepatic ALT, AST, BILIRUBIN or alkaline phosphatase measurement. For each parameter measured, some of the 3796 subjects did not have data available and are counted as missing.
Chronic Renal Failure – Pre-dialysis 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

[TSUB019B.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub019b.sas] 16JAN2018, 21:59

Exposure by Special Population; All Clinical Trials Including Open Extension

| INDICATION: Oncology | | | |
|---|---|---|---|
| Population | Category at Baseline | Patients | Person-months |
| Total | | (N=5827) | |
| Hepatic Impairment[a] | | (n=3496) | |
| ALT | | | |
| | <=ULN (normal) | 2760 | 26343.92 |
| | >ULN to <=2.5 x ULN | 522 | 5679.80 |
| | >2.5 to <=5.0 x ULN | 76 | 645.09 |
| | >5.0 to <=20.0 x ULN | 31 | 198.14 |
| | >20.0 x ULN | 10 | 46.29 |
| | Missing | 97 | |
| AST | | | |
| | <=ULN (normal) | 2640 | 24848.59 |
| | >ULN to <=2.5 x ULN | 680 | 7445.88 |
| | >2.5 to <=5.0 x ULN | 79 | 634.94 |
| | >5.0 to <=20.0 x ULN | 31 | 172.81 |
| | >20.0 x ULN | 8 | 32.23 |
| | Missing | 58 | |
| Bilirubin | | | |
| | <=ULN (normal) | 3069 | 30463.77 |
| | >ULN to <=1.5 x ULN | 116 | 1604.60 |
| | >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) | 2158 | 21809.18 |
| | >ULN to <=2.5 x ULN | 841 | 8675.68 |
| | >2.5 to <=5.0 x ULN | 195 | 1755.70 |
| | >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 | 13304.54 |
| | Moderate (CrCl>30 to <=50 mL/min) | 381 | 2378.68 |
| | Severe (CrCl<=30 mL/min) | 49 | 159.87 |
| | Missing or Other[b] | 1808 | |

Person-months may be underestimated due to missing exposure data.
[a] Of 5827 subjects in the Oncology dataset, 3496 had data measuring hepatic impairment. For each parameter measured, some subjects did not have data available and are counted as missing.
[b] Of the 3740 subjects with CrCl data, only 1932 were categorized as mild, moderate or severe with respect to renal impairment. The remaining 1808 subjects 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, EPOANE4008, 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), EPOANE3010, EPO-CAN-29

[TSUB019C.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub019c.sas] 16JAN2018, 21:59

Exposure by Special Population; All Clinical Trials Including Open Extension

| INDICATION: Autologous Blood Donation | | | |
|---|---|---|---|
| Population | Category at Baseline | Patients | 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 | |

Person-months may be underestimated due to missing exposure data.
[a] Of 402 subjects in the ABD dataset, 398 had data measuring hepatic impairment. For each parameter measured, some subjects did not have data available and are counted as missing.
[b] Of the 390 subjects with CrCl data, only 186 were categorized as mild, moderate or severe with respect to renal impairment. The remaining 204 subjects were normal or missing baseline CrCl.
ABD Studies: 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\DBR_RMP_2018\RE_RMP_2018_EU\tsub019d.sas] 16JAN2018, 21:59

Exposure by Special Population; All Clinical Trials Including Open Extension

| INDICATION: Surgery | | | |
|---|---|---|---|
| Population | Category at Baseline | Patients | 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 | |

Person-months may be underestimated due to missing exposure data.
[a] Of 1352 subjects in the Surgery dataset, 973 had data measuring hepatic impairment. For each parameter measured, some subjects did not have data available and are counted as missing.
[b] Of the 1303 subjects with CrCl data, only 723 were categorized as mild, moderate or severe with respect to renal impairment. The remaining 580 subjects were normal or missing baseline CrCl.
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)

[TSUB019E.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub019e.sas] 16JAN2018, 21:59

Exposure by Special Population; All Clinical Trials Including Open Extension

| INDICATION: MDS | | | |
|---|---|---|---|
| Population | Category at Baseline | Patients | Person-months |
| Total | | (N=112) | |
| Hepatic Impairment | | (n=109) | |
| ALT | | | |
| | <=ULN (normal) | 97 | 741.33 |
| | >ULN to <=2.5 x ULN | 9 | 53.78 |
| | >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) | 96 | 723.16 |
| | >ULN to <=2.5 x ULN | 8 | 49.08 |
| | >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 | 92 | |
| Alkaline phosphatase | | | |
| | <=ULN (normal) | 96 | 723.65 |
| | >ULN to <=2.5 x ULN | 10 | 63.28 |
| | >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=111) | |
| | Mild (CrCl>50 to <80 mL/min) | 47 | 323.81 |
| | Moderate (CrCl>30 to <=50 mL/min) | 22 | 200.08 |
| | Severe (CrCl<=30 mL/min) | 5 | 38.57 |
| | Missing or Other[b] | 37 | |

Person-months may be underestimated due to missing exposure data.
[a] Of 112 subjects in the MDS dataset, 109 had data measuring hepatic impairment. For each parameter measured, some subjects did not have data available and are counted as missing.
[b] Of the 111 subjects with CrCl data, only 74 were categorized as mild, moderate or severe with respect to renal impairment. The remaining 37 subjects were normal or missing baseline CrCl.
MDS Studies: EPOANE3018 and EPOANE3021
Note: 10 subjects who switched from PBO to EPO during the OLE are added to the EPO exposure for the duration accordingly during which they are exposed to EPO.

[TSUB019G.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tsub019g.sas] 16JAN2018, 21:59

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

# PART II: SAFETY SPECIFICATION

## Module SIV: Populations Not Studied in Clinical Trials

### SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

**Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Programme**

| **Pure red cell aplasia** | |
|---|---|
| Reason for being an exclusion criterion | 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. |
| Considered to be included as missing information | No |
| Rationale (if not included as missing information) | Considered to be an important identified risk |

| **Uncontrolled Hypertension** | |
|---|---|
| Reason for being an exclusion criterion | Hypertension is the most frequent adverse drug reaction during treatment with epoetin alfa. Patients with uncontrolled hypertension can experience a hypertensive crisis; therefore, hypertension should be controlled first before starting treatment with EPREX. |
| Considered to be included as missing information | No |
| Rationale (if not included as missing information) | Considered to be an important identified risk at the time the pivotal clincal trials were conducted. Hypertension/Hypertensive crisis has been removed as an important identified risk when aligning the RMP with GVP Module V, rev 2. |

| **Hypersensitivity** | |
|---|---|
| Reason for being an exclusion criterion | It is not appropriate to expose patients to a drug to which they have a known hypersensitivity. |

| **Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Programme** | |
|---|---|
| Considered to be included as missing information | No |
| Rationale (if not included as missing information) | EPREX is contraindicated for those who have a known sensitivity to epoetin alfa. |
| **Severe cardiac or cerebral disease** | |
| Reason for being an exclusion criterion | Patients with severe cardiac or cerebral disease are at greater risk for Thrombotic vascular events and Congestive heart failure. |
| Considered to be included as missing information | No |
| Rationale (if not included as missing information) | At the time the pivotal clinical trials were conducted, Thrombotic vascular events were considered to be important identified risks and Congestive heart failure was considered to be an important potential risk. In alignment with GVP Module V, rev 2, Thrombotic vascular events have been removed as important identified risks and Congestive heart failure has been removed as an important potential risk from the RMP. |
| **Seizures** | |
| Reason for being an exclusion criterion | Patients with a history of seizures are at risk for hypertension-associated encephalopathy. It would not be appropriate to enroll them in clinical trials. |
| Considered to be included as missing information | No |
| Rationale (if not included as missing information) | The risk of seizures was considered to be related to the important identified risk of Hypertension/Hypertensive crisis and potential for encephalopathy within that context at the time the pivotal clincal trials were conducted. Hypertension/Hypertensive crisis has been removed as an important identified risk when aligning the RMP with GVP Module V, rev 2. |
| **Pregnancy** | |
| Reason for being an exclusion criterion | It is common practice not to include pregnant women in clinical trials. |

| Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Programme | |
|---|---|
| Considered to be included as missing information | No |
| Rationale (if not included as missing information) | There are no adequate data on the use of EPREX in pregnant women. The SmPC states there are no or limited amount of data from the use of epoetin alfa in pregnant women. Studies in animals have shown reproductive toxicity. Consequently, epoetin alfa should be used in pregnancy only if the potential benefit outweighs the potential risk to the foetus. The use of epoetin alfa is not recommended in pregnant surgical patients participating in an autologous blood predonation programme. This product has been marketed for over 25 years and post-marketing data have not shown any change in benefit/risk profile with regards to pregnancy. |

## SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions or adverse reactions with a long latency. 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. ADRs with long latency may not have been detected.

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

**Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes**

| Type of Special Population | Exposure |
|---|---|
| Pregnant women | Not included in the clinical development programme |
| Breastfeeding women | Not included in the clinical development programme |
| Patients with relevant comorbidities: | |
| • Patients with hepatic impairment | 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 |

| Type of Special Population | Exposure |
|---|---|
| | were exposed to EPREX in clinical trials. |
| • Patients with renal impairment | Not applicable – indicated for CKD and CRF |
| • Patients with cardiovascular impairment | 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. |
| • Immunocompromised patients | Renal transplant patients receiving immunosuppressive therapy have been treated with EPREX in clinical trials.<br>Cancer and MDS patients in clinical trials, either as a function of the disease, or of their chemotherapy, are immunocompromised. |
| • Patients with a disease severity different from inclusion criteria in clinical trials | Not included in the clinical development programme |
| • Population with relevant different ethnic origin | Of the 15,349 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. |
| • Subpopulations carrying relevant genetic polymorphisms | Not included in the clinical development programme |

**Summary of Safety Concerns Due to Limitations of the Clinical Trial Programme**

| | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | None |

**European Union Risk Management Plan (EU-RMP)**

# EPREX® (epoeitin alfa)

# PART II: SAFETY SPECIFICATION

## Module SV: Post-authorisation Experience

### SV.1. Post-authorisation Exposure

#### SV.1.1. Method used to Calculate Exposure

The post-marketing 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 [1]

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.

Market research sources for non-study exposure data (non-clinical) are unavailable for breakdowns such as usage in children, the elderly, pregnant or breastfeeding women, severe hepatic impairment population, or renal impairment population.

#### SV.1.2. Exposure

The cumulative epoetin alfa post-marketing exposure from first product launch in 1989 through 31 August 2017 was 4,919,923 person-years (PY) (data on post-marketing 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). Market research sources for non-study exposure data (non-clinical) are unavailable for breakdowns such as usage in children, the elderly, pregnant or breastfeeding women, severe hepatic impairment population, or renal impairment population.

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

## Table SV.1: Exposure Table by Time Period and Indication, Gender, Age Group, Region

**Worldwide Epoetin Alfa Post-marketing 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 | **3,879,870** |
| 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 | **548,833** |
| 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 | **446,911** |
| 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 | **42,798** |
| HIV | 1,420 | 4 | 6 | 80 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **1,511** |
| **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** | **4,919,923** |

**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.

## Table SV.2: Exposure Table by Year and Route of Administration (in Chronic Renal Failure)

**Worldwide Post-marketing 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.

**Post-marketing (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.

**Post-marketing (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.

**Post-marketing (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.

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

# PART II: SAFETY SPECIFICATION

## Module SVI: Additional EU Requirements for the Safety Specification

### 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. EPREX is administered intravenously or subcutaneously. It is not subject to abuse when administered through regulated channels.

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

# PART II: SAFETY SPECIFICATION

## Module SVII: Identified and Potential Risks

### SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable – this is not an initial RMP

### SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable – this is not an initial RMP

**Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:**

Not applicable – this is not an initial RMP

### SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable – this is not an intial RMP

### SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

No new safety concerns have been identified since this RMP was last updated.

The important **identified** risks of Thrombotic vascular events and Hypertension/Hypertensive crisis were removed in alignment with the guidance in GVP Module V (rev 2). These risks are well-characterized, recognized, and managed within the scope of practicing healthcare professionals. These risks are adequately reflected in the SmPC, and their recognition and management have been integrated within standard clinical practice. They only require routine pharmacovigilance and routine risk minimisation measures. No safety data have emerged that would suggest a quantitative or qualitative change for these important identified risks.

The important **potential** risk of CHF was removed, considering the rationale below and in alignment with GVP Module V (rev 2):

**Epidemiology**

It is important to consider that the populations studied are at increased risk of CHF. The risk estimate of CHF in chronic kidney disease ranges from 1.5 to 50 and increases with worsening renal function. In oncology, the incidence of CHF is 70% greater than the nononcology population, with a prevalence of 17.5% to 52%. The pre-operative rate of CHF in knee/hip surgery patients is 27%, and postoperative rates range from 6.7% at 7 days to 21.3% at 1 year. Finally, in myelodysplastic syndrome, approximately 20% of patients have an ejection fraction <50%.

**Janssen Epoetin Alfa Clinical Trial Database**

There is no statistically significant increased risk of CHF with epoetin alfa compared with control groups in the randomised controlled trial populations (total N=7595) in any of the indications. The odds ratios range from 0.51 to 1.10, and all of the confidence intervals include 1, indicating a lack of statistical significance.

When pooling all of the clinical trial subjects, including uncontrolled studies and open-label extensions (total N=15,349), there were 1,562 (10.2%) events with epoetin alfa.

Overall, from the epoetin clinical trials, the rate of events is 1562/106,053.56 person-months of exposure, for a rate of approximately 1.2 per 1000 person-years.

**Epoetin Alfa Global Safety Database**

A cumulative search of the global safety database for EPREX through 31 August 2018 identified 106 spontaneous cases reporting events in the CHF Standardised MedDRA Query (narrow). Considering a cumulative postmarketing exposure of 5,068,788 person-years, the rate of events is exceedingly rare, at approximately 2.1 per 100,000 person-years.

**Epoetin Cardiovascular Outcomes Trials**

A review of large, adjudicated cardiovascular (CV) outcomes trials with epoetins have not shown a significantly increased risk of CHF when comparing high/normal vs low haemoglobin (HBG) and haematocrit (Hct) targets or compared with placebo. For example, Besarab et al studied 1,233 patients with clinical evidence of CHF or ischaemic heart disease who were undergoing haemodialysis for end-stage renal disease, who were randomized to receive epoetin to maintain a Hct of either 42% or 30% (ie, normal or low) (Besarab 1998). After 29 months, there were 183 deaths and 19 first nonfatal myocardial infarctions in the normal Hct group and 150 deaths and 14 nonfatal myocardial infarctions in the low Hct group, the difference was not statistically significant (RR=1.3; 95% CI: 0.9 to 1.9). CHF requiring hospitalization was a key secondary endpoint, which was not statistically significant different between the normal Hct group (13%) and the low Hct group (15%) (p=0.41).

In the Cardiovascular Risk Reduction by Early Anemia Treatment (CREATE) trial, Drueke et al randomly assigned 603 patients with CKD to receive epoetin treatment to a target in the normal range (13.0 to 15.0 g/dL) or subnormal range (10.5 to 11.5 g/dL) (Drueke 2006). The rate of acute heart failure was not significantly different between the 2 groups (4% vs 8%; p=0.11), nor was the mean time to worsening of New York Heart Association (NYHA) class (p=0.97). There were no changes in echocardiography findings between the groups.

In the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial investigators randomized 1,432 subjects with CKD to receive epoetin alfa to achieve a target Hb of 13.5 g/dL or 11.3 g/dL (ie, high vs low) (Singh 2006). As part of the primary composite endpoint, the rate of hospitalization for CHF was 9.0% vs 6.6%, which approached statistical significance (p=0.07). The overall rate of serious CHF was statistically higher in the high Hb group (11.2% vs 7.4%; p=0.02), although this was not part of the composite endpoint.

In the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), 4,038 patients with type 2 diabetes and CKD were assigned to darbepoetin alfa or placebo to achieve a Hb level of approximately 13 g/dL (Pferrer 2009). CHF, as part of the composite endpoint, occurred in 10.2% of the darbepoetin group compared with 11.3% in the placebo group (p=0.24).

Patient history of CHF in these 4 trials ranged from 23% to 45%, illustrating the extent of background risk in the intended patient population.

The effect of epoetins in heart failure has also been specifically studied. In the Reduction of Events by Darbepoetin Alfa in Heart Failure (RED-HF) trial, 2,278 patients with systolic heart failure and anaemia were randomized to receive either darbepoetin alfa or placebo, with a target Hb level of 13 g/dL (Swedberg 2013). First hospitalization for worsening heart failure, part of the composite primary endpoint, occurred in 27.6% of the darbepoetin subjects and 27.2% of placebo patients (p=0.92).

In addition, a meta-analysis of ESAs in heart failure in anaemia (N=663) found statistically significant improvements in exercise duration (p=0.03), NYHA functional class (p=0.0009), 6-minute walk test (p=0.01), and B-type natriuretic peptide levels (p=0.03) compared with placebo (Tehrani 2009). The authors noted that, although the most significant side effect involved in the various studies was death, they were not directly related to the effects ESAs, but rather due to causes such as complications of surgery, pneumonia, or sepsis.

Taken as a whole, these large, well-controlled clinical trials and meta-analysis that specifically evaluated CHF as part of overall CV outcomes do not definitively show a significantly increased rate of adjudicated CHF events in high vs low Hb/Hct levels or vs placebo (depending on study). The large TREAT and RED-HF studies, which included a placebo arm, provide particularly strong evidence.

**Conclusion**

The extensive patient exposures and broad populations/indications in both the clinical and postmarketing databases provide robust data sources in both the controlled and uncontrolled environments, neither of which supports an association between epoetin alfa and CHF. This is further supported by large, well-controlled and adjudicated CV outcomes trials with epoetins. Considering these data and the high background risk of the population being treated, CHF is unlikely to be associated with epoetin alfa. In addition, there are no additional pharmacovigilance activities or risk minimisation measures.

## SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

The Important Identified Risks, Important Potential Risks and Missing Information with EPREX are based on the nonclinical and clinical trial experience, as well as on post-marketing experience for some risks.

Important identified risks are:

- Pure red cell aplasia

Important potential risks are:

- Disease progression
- Survival impact

Missing Information:

- None

MedDRA version 19.1 was used to classify the clinical trials adverse event information that is summarised in this section.

## SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

**Important Identified Risk**

**Pure red cell aplasia**

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).

Evidence Source(s) and Strength of Evidence:

Pure red cell aplasia was initially identified in the post-marketing setting and is also described in the current prescribing information for EPREX.

Characterisation of the Risk - Data:

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: Chronic Renal Failure – Dialysis | | | |
|---|---|---|---|
| | Epoetin alfa (N=2046) | Non-ESA control (N=46) | Odds Ratio [a] (95% CI) |
| Randomised Controlled Trials [b] N | 97 | 46 | |
| 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%) | |

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: Chronic Renal Failure – Dialysis | | | |
|---|---|---|---|
| | Epoetin alfa (N=2046) | Non-ESA control (N=46) | Odds Ratio [a] (95% CI) |
| Hospitalised | 0 (0.00%) | 0 (0.00%) | |
| Recovered | 0 (0.00%) | 0 (0.00%) | |
| Not 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 | 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 (%) | 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%) | |
| Recovered | 0 (0.00%) | 0 (0.00%) | |
| Not 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 | 0 (0.00%) | 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 (%) | 0 (0.00%) | 0 (0.00%) | |
| Outcome (Based on Serious AEs) | 0 | 0 | |
| Fatal | 0 (0.00%) | 0 (0.00%) | |
| Hospitalised | 0 (0.00%) | 0 (0.00%) | |
| Recovered | 0 (0.00%) | 0 (0.00%) | |
| Not 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 | 0 (0.00%) | 0 (0.00%) | |
| Unknown | 0 (0.00%) | 0 (0.00%) | |
| Missing | 0 (0.00%) | 0 (0.00%) | |

[a] The stratified Mantel-Haenszel odds ratio (stratified by study) 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 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)
Note: there were no ESA non-control arms in trials therefore are being noted as NA.

[TAE03A.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tae03a.sas] 16JAN2018, 22:00

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: Chronic Renal Failure – Pre-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 (%) | 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 (%) | | | |
| Mild | 0 (0.00%) | 0 (0.00%) | |
| Moderate | 0 (0.00%) | 0 (0.00%) | |
| 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] | 5146 | 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 (%) | | | |
| Mild | 0 (0.00%) | 0 (0.00%) | |
| Moderate | 0 (0.00%) | 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) | 5610 | 325 | |
| N | | | |
| Any Treatment-Emergent Event, n (%) | 0 (0.00%) | 0 (0.00%) | |
| 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 | 0 (0.00%) | 0 (0.00%) | |
| Unknown | 0 (0.00%) | 0 (0.00%) | |
| Missing | 0 (0.00%) | 0 (0.00%) | |

[a] The stratified Mantel-Haenszel odds ratio (stratified by study) 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 – Pre-dialysis 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
Note: there were no ESA non-control arms in trials therefore are being noted as NA.

[TAE03B.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tae03b.sas] 16JAN2018, 22:00

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 | | |
|---|---|---|---|
| | 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 | | | |
|---|---|---|---|
| | Epoetin alfa (N=5827) | Non-ESA control (N=4719) | Odds Ratio [a] (95% CI) |

[a] The stratified Mantel-Haenszel odds ratio (stratified by study) 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, EPOANE3010
[c] Includes EPOANE4008
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, EPOANE4008, 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, EPOANE3010
Note: there were no ESA non-control arms in trials therefore are being noted as NA.

[TAE03C.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tae03c.sas] 09FEB2018, 13:59

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: 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 (%) | 0 (0.00%) | 0 (0.00%) | N/A |
| Outcome (Based on Serious AEs) | N/A | N/A | |
| Severity, n (%) | | | |
| Mild | 0 (0.00%) | 0 (0.00%) | |
| Moderate | 0 (0.00%) | 0 (0.00%) | |
| Severe | 0 (0.00%) | 0 (0.00%) | |
| Missing | 0 (0.00%) | 0 (0.00%) | |
| Combined (All Trials) N | 402 | 242 | |
| Any Treatment-Emergent Event, n (%) | 0 (0.00%) | 0 (0.00%) | |
| Outcome (Based on Serious AEs) | N/A | N/A | |
| Severity, n (%) | | | |
| Mild | 0 (0.00%) | 0 (0.00%) | |
| Moderate | 0 (0.00%) | 0 (0.00%) | |
| Severe | 0 (0.00%) | 0 (0.00%) | |
| Missing | 0 (0.00%) | 0 (0.00%) | |

[a] The stratified Mantel-Haenszel odds ratio (stratified by study) 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 Studies: CC 2574-P-159, CC 2574-P-165, CC 2574-P-166, H87-017, H87-036, I88-027, I88-058.
Note: there were no ESA non-control arms in trials therefore are being noted as NA.

[TAE03D.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tae03d.sas] 16JAN2018, 22:01

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: 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 (%) | 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 (%) | | | |
| Mild | 0 (0.00%) | 0 (0.00%) | |
| Moderate | 0 (0.00%) | 0 (0.00%) | |
| 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] | 145 | 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 (%) | | | |
| Mild | 0 (0.00%) | 0 (0.00%) | |
| Moderate | 0 (0.00%) | 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 (%) | 0 (0.00%) | 0 (0.00%) | |
| 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 | 0 (0.00%) | 0 (0.00%) | |
| Unknown | 0 (0.00%) | 0 (0.00%) | |
| Missing | 0 (0.00%) | 0 (0.00%) | |

[a] The stratified Mantel-Haenszel odds ratio (stratified by study) 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 Studies: EPO-APO2-474, EPO-INT-34 (EPO-AP02-478), CEO-C04, H87-083, J89-001, M92-011, N93-057, PR97-19-002 (spine)
Note: there were no ESA non-control arms in trials therefore are being noted as NA.

[TAE03E.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tae03e.sas] 16JAN2018, 22:01

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=112) | 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) | 112 | 53 | |
| N | | | |
| Any Treatment-Emergent Event, n (%) | 1 (0.89%) | 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 (0.89%) | 1 (1.89%) | |
| Recovered | 0 (0.00%) | 0 (0.00%) | |
| N/A | 0 (0.00%) | 0 (0.00%) | |
| Severity, n (%) | | | |
| Grade=1 | 1 (0.89%) | 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%) | |

[a] The stratified Mantel-Haenszel odds ratio (stratified by study) was used.
[b] Includes EPOANE3018 and EPOANE3021
MDS Studies: EPOANE3018 and EPOANE3021
Note: 10 subjects who switched from PBO to EPO during the OLE are added to the EPO exposure for the duration accordingly during which they are exposed to EPO.

[TAE03G.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tae03g.sas] 16JAN2018, 22:01

MedDRA terms used in database search:

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.

Characterisation of the Risk – Discussion

Pure red cell aplasia is a risk identified from post-marketing 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.

An immunogenicity surveillance registry (Study EPOANE4014) 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 EPOANE4014 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).

Risk Factors and Risk Groups:

***Chronic Renal Failure***

Pure red cell aplasia has been reported in patients with CRF who were receiving epoetin alfa by SC administration. Risk factors for Ab-mediated PRCA can be related to both patient and product (erythropoietin). Patient-related factors associated with developing Ab-mediated PRCA include skin reactions, immune status, and treatment history. Product-related factors that could impact immunogenicity include sequence variations in proteins, degree and nature of protein glycosylation, manufacturing process, handling and storage, and components and properties of the product formulation (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.

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 epoetin treatment. Very rarely, cases have been reported with IV epoetin use as well. Cases also have been reported in patients with hepatitis C treated with interferon and ribavirin, when ESAs are used concomitantly. Epoetin alfa is not approved in the management of anaemia associated with hepatitis C.

Impact on the Risk-Benefit Balance of the Product:

The observed incidence and severity of PRCA have not had a significant impact on the risk-benefit balance of the product. The SmPC and PL provide information to the prescriber and patient on how to manage the risk.

Public Health Impact:

The increase in Ab-positive PRCA cases reported between 1999 and 2003 has been associated with a specific epoetin alfa formulation/presentation (PS-80 uncoated stopper pre-filled syringes in 1,000 IU and 10,000 IU strengths) used SC in CKD/CRF patients. The worldwide withdrawal of this formulation/presentation was completed in March 2004 and PS-80 coated stopper PFS for all strengths have been manufactured since April 2003. The annual RRs of Ab-positve PRCA in CKD/CRF patients for all presentations/formulations and routes of administration since 2004 remain well below the historic peak in 2002.

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). Considering the rarity of events from clinical trials (n=2) and similar incidence in non-ESA comparators, and considering the low rate of PRCA since the removal of the PS-80 PFS uncoated stopper formulation, the overall public health impact is, therefore, considered limited.

Annex 1 MedDRA term:

Not applicable

**Important Potential Risk**

**Disease Progression**

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.

Evidence Source(s) and Strength of Evidence:

Cases of disease progression have been reported in completed clinical trials and are also described in the current prescribing information for EPREX.

Characterisation of the Risk - Data:

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 (%) | 294 (5.52%) | 250 (5.30%) | 1.00 (0.81,1.24) |
| Outcome (Based on Serious AEs) | 75 | 48 | |
| Fatal | 12 (0.23%) | 5 (0.11%) | |
| Hospitalised | 0 (0.00%) | 0 (0.00%) | |

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) |
| 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%) | 7 (0.15%) | |
| Grade=2 | 35 (0.66%) | 27 (0.57%) | |
| Grade=3 | 117 (2.20%) | 79 (1.67%) | |
| Grade>=4 | 1 (0.02%) | 1 (0.02%) | |
| Unknown | 134 (2.52%) | 136 (2.88%) | |
| | | | |
| Trials without control [c] | 504 | 0 | |
| N | | | |
| Any Treatment-Emergent Event, n (%) | 57 (11.3%) | 0 (0.00%) | N/A |
| Outcome (Based on Serious AEs) | 39 | 0 | |
| Fatal | 28 (5.56%) | 0 (0.00%) | |
| Hospitalised | 0 (0.00%) | 0 (0.00%) | |
| Not Recovered | 9 (1.79%) | 0 (0.00%) | |
| Recovered | 1 (0.20%) | 0 (0.00%) | |
| N/A | 1 (0.20%) | 0 (0.00%) | |
| Severity, n (%) | | | |
| Grade=1 | 4 (0.79%) | 0 (0.00%) | |
| Grade=2 | 7 (1.39%) | 0 (0.00%) | |
| Grade=3 | 31 (6.15%) | 0 (0.00%) | |
| Grade>=4 | 14 (2.78%) | 0 (0.00%) | |
| Unknown | 1 (0.20%) | 0 (0.00%) | |
| | | | |
| Combined (All Trials) | 5827 | 4719 | |
| N | | | |
| Any Treatment-Emergent Event, n (%) | 351 (6.02%) | 250 (5.30%) | |
| Outcome (Based on Serious AEs) | 114 | 48 | |
| Fatal | 40 (0.69%) | 5 (0.11%) | |
| Hospitalised | 0 (0.00%) | 0 (0.00%) | |
| Not Recovered | 38 (0.65%) | 17 (0.36%) | |
| Recovered | 19 (0.33%) | 15 (0.32%) | |
| N/A | 17 (0.29%) | 11 (0.23%) | |
| Severity, n (%) | | | |
| Grade=1 | 11 (0.19%) | 7 (0.15%) | |
| Grade=2 | 42 (0.72%) | 27 (0.57%) | |
| Grade=3 | 148 (2.54%) | 79 (1.67%) | |
| Grade>=4 | 15 (0.26%) | 1 (0.02%) | |
| Unknown | 135 (2.32%) | 136 (2.88%) | |

[a] The stratified Mantel-Haenszel odds ratio (stratified by study) 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, EPOANE3010
[c] Includes EPOANE4008
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, EPOANE4008, 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, EPOANE3010
Note: there were no ESA non-control arms in trials therefore are being noted as NA.

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=112) | Non-ESA control (N=53) | Odds Ratio [a] (95% CI) |
| Randomised Controlled Trials [b] | 102 | 53 | |
| N | | | |
| 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) | 112 | 53 | |
| N | | | |
| Any Treatment-Emergent Event, n (%) | 4 (3.57%) | 1 (1.89%) | |
| Outcome (Based on Serious AEs) | 4 | 1 | |
| Fatal | 1 (0.89%) | 0 (0.00%) | |
| Hospitalised | 0 (0.00%) | 0 (0.00%) | |
| Not Recovered | 3 (2.68%) | 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 (1.79%) | 0 (0.00%) | |
| Grade=3 | 1 (0.89%) | 1 (1.89%) | |
| Grade>=4 | 1 (0.89%) | 0 (0.00%) | |
| Unknown | 0 (0.00%) | 0 (0.00%) | |

[a] The stratified Mantel-Haenszel odds ratio (stratified by study) was used.
[b] Includes EPOANE3018 and EPOANE3021
MDS Studies: EPOANE3018 and EPOANE3021
Note: 10 subjects who switched from PBO to EPO during the OLE are added to the EPO exposure for the duration accordingly during which they are exposed to EPO.

[TAE07G.rtf] [JNJ-7472179\Z_RMP\DBR_RMP_2018\RE_RMP_2018_EU\tae07g.sas] 16JAN2018, 22:01

MedDRA terms used in database search: Condition aggravated, disease progression, malignant neoplasm progression, neoplasm progression

Characterisation of the Risk - Discussion:

***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 evaluated the impact of epoetin alfa on tumour outcome including PFS and survival in an appropriately designed clinical trial (Trial EPOANE3010), the results of which are included in the risk tables.

Among the 5,827 adult patients treated in all cancer clinical trials, there were 351 (6.02%) treatment-emergent disease progression event among patients treated with EPREX and 250 (5.30%) among non-ESA-treated patients. The largest number among patients treated with EPREX were considered Grade 3 (148, 2.54%) and the largest number among non-ESA-treated patients were also Grade 3 (79 1.67%). The severity was unknown for a substantial number of patients in both groups.

***Myelodysplastic Syndrome***

Among the 112 adult patients treated in all cancer clinical trials, there were 4 (3.57%) treatment-emergent disease progression event among patients treated with EPREX and 1 (1.89%) among non-ESA-treated patients. The largest number among patients treated with EPREX were considered Grade 2 (2, 1.79%) and the largest number among non-ESA-treated patients was Grade 3 (1, 1.89%).

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.

Risk Factors and Risk Groups:

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

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 Risk-benefit Balance of the Product:

The observed incidence and severity of disease progression events have not had a significant impact on the risk-benefit balance of the product. The SmPC and PL provide information to the prescriber and patient on how to manage the risk.

Public Health Impact:

Decreased PFS time in patients with cancer.

Annex 1 MedDRA term:

Not applicable

**Important Potential Risk**

**Survival Impact**

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.

Evidence Source(s) and Strength of Evidence:

Survival data were not routinely collected in all trials for all indications. Increased mortality was observed in some cancer and chronic renal failure trials.

Characterisation of the Risk – Data:

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.

Characterisation of the Risk – Discussion:

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.

Study EPOANE3010, a randomized, open-label, multicenter study was conducted in 2,098 anemic women with metastatic breast cancer, who received first line or second line chemotherapy. At the time of clinical data cutoff, the median progression free survival (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. Significantly fewer patients received RBC transfusions in the epoetin alfa plus SOC arm (5.8% versus 11.4%); however, significantly more patients had TVEs in the

epoetin alfa plus SOC arm (2.8% versus 1.4%). At the final analysis, 1653 deaths were reported. Median overall survival in the epoetin alfa plus SOC group was 17.8 months compared with 18.0 months in the SOC alone group (HR 1.07, 95% CI: 0.97, 1.18). The median time to progression (TTP) based on investigator-determined progressive disease (PD) was 7.5 months in the epoetin alfa plus SOC group and 7.5 months in the SOC group (HR 1.099, 95% CI: 0.998, 1.210). The median TTP based on IRC-determined PD was 8.0 months in the epoetin alfa plus SOC group and 8.3 months in the SOC group (HR 1.033, 95% CI: 0.924, 1.156).

Risk Factors and Risk Groups:

Survival data were not routinely collected in all trials for all indications. Increased mortality was observed in some cancer and CRF trials. However, survival in patients with cancer mainly depends on the underlying tumour type and patients in different cancer trials had very different tumour types.

Preventability:

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.

Impact on the Risk-benefit Balance of the Product:

The limited data, derived mainly from treatment in cancer, do not indicate any impact on the risk-benefit balance.

Public Health Impact:

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.

Annex 1 MedDRA term:

Not applicable

### SVII.3.2. Presentation of the Missing Information

Not applicable

# PART II: SAFETY SPECIFICATION

## Module SVIII: Summary of the Safety Concerns

**Table SVIII.1: Summary of Safety Concerns**

| |
|---|
| **Important identified risks** |
| Pure red cell aplasia |
| **Important potential risks** |
| Disease progression |
| Survival impact |
| **Missing information** |
| None |

# PART III: PHARMACOVIGILANCE PLAN (Including Post-Authorisation Safety Studies

## III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

| **Specific Adverse Reaction Follow-up Questionnaires** | |
|---|---|
| Safety Concern | Purpose/Description |
| Pure red cell aplasia | Two Targeted Follow-up Questionnaires: One to capture information at the initial loss of efficacy, and one for follow-up information after PRCA diagnosis |

**Other Forms of Routine Pharmacovigilance Activities**

| Activity | Objective/Description | Milestones |
|---|---|---|
| Annual Immunogenicity Report; Independent Safety Advisory Committee adjudication (ISAC); PRCA pharmacovigilance plan | The primary objective is to estimate the incidence of anti-human erythropoietin Ab and anti-erythropoetin PRCA in patients with IV or SC exposure to ESAs who have CKD. Data obtained can provide information regarding general adherence to instructions in the SmPC for routine antibody testing and bone marrow biopsy in unexplained loss of efficacy. | Annual |

## III.2. Additional Pharmacovigilance Activities

| Activity | Objective/Description | Milestones |
|---|---|---|
| None | | |

## III.3. Summary Table of Additional Pharmacovigilance Activities

**Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities**

Not applicable

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

# PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

## Table Part IV.1: Planned and Ongoing Post-Authorisation Efficacy Studies That Are Conditions of the Marketing Authorisation or That Are Specific Obligations

| Study Status | Summary of Objectives | Efficacy Uncertainties Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| Efficacy Studies which are conditions of the marketing authorisations | | | | |
| None | | | | |
| Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances | | | | |
| None | | | | |

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

# PART V: RISK MINIMISATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

## Risk Minimisation Plan

## V.1. Routine Risk Minimisation Measures

**Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern**

| Safety Concern | Routine Risk Minimisation Activities |
|---|---|
| Pure red cell aplasia | Routine risk communication:<br>SmPC Section 4.3<br>SmPC Section 4.4<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Monitor haemoglobin levels closely (SmPC Section 4.4) |
| Disease progression | Routine risk communication:<br>SmPC Section 4.4<br>SmPC Section 5.1<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Monitor haemoglobin levels closely (SmPC Section 4.4) |
| Survival impact | Routine risk communication:<br>SmPC Section 4.4<br>SmPC Section 5.1<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>None |

## V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

### V.2.1. Removal of Additional Risk Minimisation Activities

| Activity | Safety Concern(s) Addressed/Rationale for the Removal of Additional Risk Minimisation Activity |
|---|---|
| Not applicable | |

## V.3. Summary of Risk Minimisation Measures and Pharmacovigilance Activities

**Table Part V.3: Summary Table of Risk Minimisation Activities and Pharmacovigilance Activities by Safety Concern**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| Pure red cell aplasia | Routine risk communication:<br>SmPC Section 4.3<br>SmPC Section 4.4<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Monitor haemoglobin levels closely (SmPC Section 4.4)<br>Additional risk minimisation measures:<br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>TFUQs<br>Annual Immunogenicity Report; Independent Safety Advisory Committee adjudication (ISAC); PRCA pharmacovigilance plan<br>Additional pharmacovigilance activities:<br>None |
| Disease progression | Routine risk communication:<br>SmPC Section 4.4<br>SmPC Section 5.1<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Monitor haemoglobin levels closely (SmPC Section 4.4)<br>Additional risk minimization measures:<br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None<br>Additional pharmacovigilance activities:<br>None |
| Survival impact | Routine risk communication:<br>SmPC Section 4.4<br>SmPC Section 5.1<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None<br>Additional pharmacovigilance activities:<br>None |

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| | Additional risk minimization measures:<br>None | |

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

# PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

## Summary of Risk Management Plan for EPREX (erythropoietin alfa)

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

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

Important new concerns or changes to the current ones will be included in updates of EPREX's RMP.

## I. The Medicine and What it is Used For

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

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

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

Important risks of EPREX, together with measures to minimise such risks and the proposed studies for learning more about EPREX's risks, are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

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

## II.A. List of Important Risks and Missing Information

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

| **List of Important Risks and Missing Information** | |
|---|---|
| Important identified risks | Pure red cell aplasia |
| Important potential risks | Disease progression<br>Survival impact |
| Missing information | None |

## II.B. Summary of Important Risks

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

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

| | |
|---|---|
| | SmPC Section 5.1<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>None<br>Additional risk minimization measures:<br>None |

## II.C. Post-authorisation Development Plan

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

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

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

There are no studies required for EPREX.

# PART VII: ANNEXES

## Table of Contents

## Annex 1: Eudravigilance Interface

(electronic only)

# Annex 2: Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programme

## Table 1 Annex II: Planned and Ongoing Studies

Not applicable

## Table 2 Annex II: Completed Studies

| Study | Summary of Objectives | Safety Concerns Addressed | Date of Final Study Report Submission Link to Report |
|---|---|---|---|
| Trial EPOANE3010<br>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<br>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 | 01 June 2017 |
| Trial EPOANE4014<br>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<br>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 | Final study report submitted<br>25 Jan 2012 |
| Trial EPOANE4008<br>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<br>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 | Final study report submitted 31 Mar 2010 |

| Study | Summary of Objectives | Safety Concerns Addressed | Date of Final Study Report Submission Link to Report |
|---|---|---|---|
| Trial EPOANE4076[a]<br>A Prospective, Immunogenicity Surveillance Registry of Erythropoiesis-Stimulating Agents with Subcutaneous Exposure in Thailand<br>Category 3 | Estimate the incidence of anti-human erythropoiesis and anti-erythropoietin PRCA in patients using any ESA by the SC route. | PRCA | 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 EPOANE4014 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.

# Annex 3: Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan

**Table of Contents**

**Part A:** Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable

**Part B:** Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable

**Part C:** Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority

Not applicable

# Annex 4: Specific Adverse Drug Reaction Follow-up Forms

## Table of Contents

## Follow-up Forms

Decreased therapeutic response or loss of efficacy

Pure red cell aplasia


# QUESTIONNAIRE FOR DECREASED THERAPEUTIC RESPONSE (DTR) OR LOSS OF EFFICACY (LOE)

EPO-IMU-001

COVER

EPO-IMU-001_LOE-2_(28NOV2011).fm

**Janssen Research & Development, LLC**

**Global Medical Safety**

Protocol EPO-IMU-001

| PATIENT INITIALS | DATE | GLOBAL AE #: |
|---|---|---|
| | d d m o n y y | |

## STANDARD QUESTIONNAIRE FOR DECREASED THERAPEUTIC RESPONSE (DTR) OR LOSS OF EFFICACY (LOE)

*This questionnaire is to be used in conjunction with the standard case intake of adverse event reports so that all necessary data points will be collected.*

REPORTER INFORMATION:

**Name:** _____

**Address:** _____

**Phone:** _____ **Fax:** _____

**Email:** _____

## DEMOGRAPHICS

**Sex:**

○ 1 Male ○ 2 Female

**Race:** ○ 96 Unknown

○ 1 White ○ 2 Black ○ 3 Asian ○ 99 Other: _____

**1. What was the indication for first use of epoetin in this patient?** (Answer Yes or No for each.)

**Renal Anemia** ..... ○ 2 Yes* ○ 1 No

*If yes - Fill in one choice below.

○ 1 Pre-Dialysis Renal Failure ○ 2 1 Peritoneal Dialysis ○ 3 Hemodialysis
○ 94 None
○ 99 Other, specify:_____

**Cancer** ..... ○ 2 Yes** ○ 1 No

**If yes, Specify Type or Reason:_____

**Unknown**..... ○ 2 Yes ○ 1 No

**Other**..... ○ 2 Yes*** ○ 1 No

***If yes, Specify:_____

**2. At the time of LOE, patient was:** (Choose one only.)

○ 1 Pre-Dialysis Renal Failure ○ 2 1 Peritoneal Dialysis ○ 3 Hemodialysis ○ Normal Renal Function

1

EPO-IMU-001_LOE-2_(28NOV2011).fm

**Janssen Research & Development, LLC**

**Global Medical Safety**

Protocol EPO-IMU-001

GLOBAL AE #:

**3. What was the date of first suspicion of Loss (Lack) of Effect**

**Loss (Lack) of Effect?** . . . . . [ ] [ ] [ ] [ ] [ ] [ ] [ ] (d d m o n y y)

**4. Did the patient ever respond to epoetin treatment?** . . . . . O$_2$ Yes O$_1$ No O$_{98}$ Unknown

a) What was the Hgb value at the start of treatment: . . . . . [ ] O g/dL$_{(200)}$ O g/L$_{(100)}$ O mmol/L$_{(106)}$

b) What was the Hgb value at the start of Loss (Lack) of Effect? . [ ] O g/dL$_{(200)}$ O g/L$_{(100)}$ O mmol/L$_{(106)}$

c) Did the Hgb ever increase more than 2 g/dL? . . . . . O$_2$ Yes O$_1$ No O$_{98}$ Unknown

d) Were red blood cell transfusions required before epoetin therapy? O$_2$ Yes O$_1$ No O$_{98}$ Unknown

If yes, did RBC transfusions decrease during epoetin therapy?. . O$_2$ Yes O$_1$ No O$_{98}$ Unknown

**5. Was a Complete Blood Count performed at the time of LOE?**

O$_2$ Yes* O$_1$ No O$_{98}$ Unknown

***** *If Yes, list below most recent available results at the time of suspected LOE.*

Complete by filling in date, values, and units for all labs listed below. If lab was not done mark 'ND'.

Date of Sample: . . . . . [ ] [ ] [ ] [ ] [ ] [ ] [ ] (d d m o n y y)

| | | | | | |
|---|---|---|---|---|---|
| (1245) Total Leukocyte Count (WBC) . . . . . | [ ] | O x10$^9$/L$_{(116)}$ | O K/µL$_{(939)}$ | O x10$^3$/mm$^3$$_{(965)}$ | |
| | | O GI/L$_{(114)}$ | O /cu mm$_{(803)}$ | O /µL$_{(403)}$ | |
| (1200) Total Erythrocyte Count (RBC) . . . . . | [ ] | O x10$^{12}$/L$_{(115)}$ | O M/µL$_{(938)}$ | O x10$^6$/cu mm$_{(802)}$ | |
| | | O TI/L$_{(113)}$ | | | |
| (1075) Hemoglobin . . . . . | [ ] | O g/dL$_{(200)}$ | O g/L$_{(100)}$ | O mmol/L$_{(106)}$ | |
| (1070) Hematocrit . . . . . | [ ] | O %$_{(902)}$ | O Fraction of 1.0$_{(911)}$ | | |
| (1110) MCV (Mean Corpuscular Volume) . . . . . | [ ] | O fL$_{(700)}$ | O cu microns$_{(809)}$ | | |
| (1055) MCH (Mean Corpuscular Hemoglobin) . . . . . | [ ] | O pg$_{(604)}$ | O fmol$_{(701)}$ | | |
| (1050) MCHC (Mean Corpuscular Hemoglobin Concentration) . . . . . | [ ] | O g/dL$_{(200)}$ | O g/L$_{(100)}$ | O %$_{(902)}$ | O mmol/L$_{(106)}$ |
| (1170) Platelet Count . . . . . | [ ] | O x10$^9$/L$_{(116)}$ | O K/µL$_{(939)}$ | O x10$^3$/mm$^3$$_{(965)}$ | |
| | | O GI/L$_{(114)}$ | O /cu mm$_{(803)}$ | O /µL$_{(403)}$ | |

2

EPO-IMU-001_LOE-2_(28NOV2011).fm

**Janssen Research & Development, LLC**

**Global Medical Safety**

Protocol EPO-IMU-001

| GLOBAL AE #: |
|---|
| |

**6. Was a reticulocyte performed at the time of LOE?**

O$_2$ Yes* O$_1$ No O$_{98}$ Unknown

**If Yes, list below most recent available results at the time of suspected LOE.*

Complete by filling in date, values, and units for all labs listed below. If lab was not done mark 'ND'.

Date of Sample: . . . . . [ ][ ] d d [ ][ ][ ] m o n [ ][ ] y y

(1210) Reticulocyte % . . . . . [_____] O %$_{(902)}$ O Fraction of 1.0$_{(911)}$ Normal Range [_____]

(1210) Reticulocyte Count (absolute) . [_____] O x10$^9$/L$_{(116)}$ O x10$^3$/cu mm$_{(801)}$ O /cu mm$_{(803)}$ Normal Range [_____]

**7. What brand of epoetin was the patient taking at the time of LOE?** *(Fill in one.)*

O$_1$ **Eprex®** O$_2$ **Epoxitin®** O$_3$ **Espo®** O$_4$ **Epopen®** O$_5$ **Globuren®** O$_6$ **Erypo®**
O$_7$ **Procrit®** O$_8$ **Epogen®** O$_9$ **Culat®** O$_{10}$ **Recormon®** O$_{11}$ **NeoRecormon®** O$_{12}$ **Recopen®**
O$_{13}$ **Epogin®** O$_{14}$ **Eratin®** O$_{15}$ **Aranesp®** O$_{16}$ **Haemax®** O$_{98}$ **Unknown**
O$_{99}$ **Other, specify:**_____

*Please provide information below. Provide separate records when routes changed and detailed start and stop dates if available.*

| DOSE | ROUTE *Fill in all that apply.* | FREQUENCY *(x/week) or (x/month)* | START DATE | LOT NUMBER |
|---|---|---|---|---|
| 1. _____<br>O$_1$ Pre-fill Syringe<br>O$_2$ Single-Use Vial<br>O$_3$ Multi-Use Vial<br>O$_{99}$ Other, specify:<br>_____<br>O$_{98}$ Unknown | O$_1$ Intravenous (IV)<br>O$_2$ Subcutaneous<br>O$_{98}$ Unknown | _____ | Start date:<br>[ ][ ] d d [ ][ ][ ] m o n [ ][ ] y y<br>Stop date:<br>[ ][ ] d d [ ][ ][ ] m o n [ ][ ] y y<br>***OR*** O$_{98}$Unknown | |
| 2. _____<br>O$_1$ Pre-fill Syringe<br>O$_2$ Single-Use Vial<br>O$_3$ Multi-Use Vial<br>O$_{99}$ Other, specify:<br>_____<br>O$_{98}$ Unknown | O$_1$ Intravenous (IV)<br>O$_2$ Subcutaneous<br>O$_{98}$ Unknown | _____ | Start date:<br>[ ][ ] d d [ ][ ][ ] m o n [ ][ ] y y<br>Stop date:<br>[ ][ ] d d [ ][ ][ ] m o n [ ][ ] y y<br>***OR*** O$_{98}$Unknown | |

**Janssen Research & Development, LLC**

**Global Medical Safety**

Protocol EPO-IMU-001

| GLOBAL AE #: |
|---|
| |

***Question #7 continued.***

| DOSE | ROUTE *Fill in all that apply.* | FREQUENCY *(x/week)* | START DATE | LOT NUMBER |
|---|---|---|---|---|
| 3. _____<br>O1 Pre-fill Syringe<br>O2 Single-Use Vial<br>O3 Multi-Use Vial<br>O99 Other, specify: _____<br>O98 Unknown | O1 Intravenous (IV)<br>O2 Subcutaneous<br>O98 Unknown | _____ | Start date: d d m o n y y<br>Stop date: d d m o n y y<br>***OR*** O98 Unknown | |
| 4. _____<br>O1 Pre-fill Syringe<br>O2 Single-Use Vial<br>O3 Multi-Use Vial<br>O99 Other, specify: _____<br>O98 Unknown | O1 Intravenous (IV)<br>O2 Subcutaneous<br>O98 Unknown | _____ | Start date: d d m o n y y<br>Stop date: d d m o n y y<br>***OR*** O98 Unknown | |

**8. Were other epoetins taken before LOE?**

O2 Yes* O1 No O98 Unknown

**Please provide information below. Provide separate records when routes changed and detailed start and stop dates, if available.*

| BRAND NAME | START DATE | STOP DATE |
|---|---|---|
| 1. _____<br>_____ | d d m o n y y | d d m o n y y<br>***OR*** O98 Unknown |
| 2. _____<br>_____ | d d m o n y y | d d m o n y y<br>***OR*** O98 Unknown |

**9. Do you suspect Pure Red Cell Aplasia (PRCA):** O2 Yes O1 No

**Janssen Research & Development, LLC**
**Global Medical Safety**
Protocol EPO-IMU-001

| GLOBAL AE #: |
|---|
| |

**10. Has a bone marrow examination (biopsy and / or aspirate) been performed?**
$O_2$ Yes* $O_1$ No
**If Yes, please provide information below and provide a copy of the bone marrow biopsy report. Please remove patient identifiers.*

| DATE OF TEST | TEST | RESULT |
|---|---|---|
| d d m o n y y<br>**OR** $O_{98}$ Unknown | $O_1$ Biopsy<br>$O_2$ Aspirate<br>$O_{98}$ Unknown | $O_3$ Suggestive of Pure Red Cell Aplasia<br>$O_4$ Not suggestive of Pure Red Cell Aplasia<br>$O_{98}$ Unknown<br>$O_{99}$ Other: _____ |
| DATE OF TEST | TEST | RESULT |
| d d m o n y y<br>**OR** $O_{98}$ Unknown | $O_1$ Biopsy<br>$O_2$ Aspirate<br>$O_{98}$ Unknown | $O_3$ Suggestive of Pure Red Cell Aplasia<br>$O_4$ Not suggestive of Pure Red Cell Aplasia<br>$O_{98}$ Unknown<br>$O_{99}$ Other: _____ |

**11. Has antibody testing been performed on this patient?** $O_2$ Yes* $O_1$ No $O_{98}$ Unknown
**If Yes, provide information below for all antibody tests performed.*

| DATE OF TEST | METHOD | RESULT | LAB |
|---|---|---|---|
| d d m o n y y | $O_1$ Immunoprecipitation (IP)<br>$O_2$ Enzyme-linked Immunoassay (ELISA)<br>$O_3$ Biacore<br>$O_4$ Neutralization Bioassay<br>$O_{98}$ Unknown<br>$O_{99}$ Other:_____ | $O_2$ Positive,<br>Titer: ____ : ____<br>(highest positive serum dilution)<br>$O_1$ Negative<br>$O_3$ Borderline<br>$O_{98}$ Unknown | Name: _____<br>Address:_____<br>_____<br>Phone: _____ |
| DATE OF TEST | METHOD | RESULT | LAB |
| d d m o n y y | $O_1$ Immunoprecipitation (IP)<br>$O_2$ Enzyme-linked Immunoassay (ELISA)<br>$O_3$ Biacore<br>$O_4$ Neutralization Bioassay<br>$O_{98}$ Unknown<br>$O_{99}$ Other:_____ | $O_2$ Positive,<br>Titer: ____ : ____<br>(highest positive serum dilution)<br>$O_1$ Negative<br>$O_3$ Borderline<br>$O_{98}$ Unknown | Name: _____<br>Address:_____<br>_____<br>Phone: _____ |

5

EPO-IMU-001_LOE-2_(28NOV2011).fm

**Janssen Research & Development, LLC**

**Global Medical Safety**

Protocol EPO-IMU-001

| GLOBAL AE #: |
|---|
| |

## MEDICAL AND MEDICATION HISTORY

**12. Within 3 months of LOE did the patient have any of the following conditions?**

| *Fill Yes, No, or Unknown for each.* | YES (2) | NO (1) | UNKNOWN (98) | If yes, fill in value with unit or comment. |
|---|---|---|---|---|
| Parvovirus B19 infection (IgM) | ○ | ○ | ○ | |
| Recent Hepatitis A (confirmed by IgM antibody response) | ○ | ○ | ○ | |
| Recent or Chronic Hepatitis B | ○ | ○ | ○ | |
| Recent or Chronic Hepatitis C | ○ | ○ | ○ | |
| Thymoma confirmed by Chest CT Scan | ○ | ○ | ○ | |
| Iron Deficiency | ○ | ○ | ○ | |
| Folate Deficiency | ○ | ○ | ○ | |
| Vitamin B12 Deficiency | ○ | ○ | ○ | |
| Aluminum Intoxication | ○ | ○ | ○ | |
| Hyperparathyroidism | ○ | ○ | ○ | |

**Janssen Research & Development, LLC**

**Global Medical Safety**

Protocol EPO-IMU-001

| GLOBAL AE #: |
|---|
| |

| MEDICAL AND MEDICATION HISTORY | | | | |
|---|---|---|---|---|
| ***Question #12 continued.*** | | | | |
| ***Fill Yes, No, or Unknown for each.*** | YES (2) | NO (1) | UNKNOWN (98) | If yes, fill in value with unit or comment. |
| Haemolysis | ○ | ○ | ○ | |
| Haemoglobinopathy | ○ | ○ | ○ | |
| Leukemia | ○ | ○ | ○ | |
| Lymphoma | ○ | ○ | ○ | |
| HIV (Human Immuno Deficiency Viruses) | ○ | ○ | ○ | |
| Infection or Inflammation - *If yes, specify:*_____ | ○ | ○ | ○ | |
| Autoimmune Disease - *If yes, specify:*_____ | ○ | ○ | ○ | |
| Recent or Chronic Clinically Significant Blood Loss (internal or external) If yes, specify source of blood loss: _____ | ○ | ○ | ○ | |
| Other, specify:_____ | ○ | ○ | | |

**Janssen Research & Development, LLC**

**Global Medical Safety**

Protocol EPO-IMU-001

| GLOBAL AE #: |
|---|
| |

## MEDICATIONS

**13. Did the patient receive any of the following medications that may be associated with Pure Red Cell Aplasia or LOE within one year prior to the onset of suspected LOE?**

○$_2$ Yes* ○$_1$ No ○$_{98}$ Unknown

**If Yes, fill in all that apply. If circle filled in, provide treatment medication start date information. If continuing, fill in circle. If treatment medication stopped, fill in stop date.*

| MEDICATIONS | START DATE | STOP DATE |
|---|---|---|
| ○$_1$ Allopurinol | d d m o n y y | d d m o n y y ***OR*** ○$_1$ Continuing |
| ○$_2$ Alpha-Methyldopa Dop (Aldomet) | d d m o n y y | d d m o n y y ***OR*** ○$_1$ Continuing |
| ○$_3$ Anti-thymocyte preparations | d d m o n y y | d d m o n y y ***OR*** ○$_1$ Continuing |
| ○$_4$ Azathioprine | d d m o n y y | d d m o n y y ***OR*** ○$_1$ Continuing |
| ○$_5$ Aztreonam | d d m o n y y | d d m o n y y ***OR*** ○$_1$ Continuing |
| ○$_6$ Carbamazepine | d d m o n y y | d d m o n y y ***OR*** ○$_1$ Continuing |
| ○$_7$ Cephalothin | d d m o n y y | d d m o n y y ***OR*** ○$_1$ Continuing |
| ○$_8$ Chloramphenicol | d d m o n y y | d d m o n y y ***OR*** ○$_1$ Continuing |
| ○$_{35}$ Chloroquin | d d m o n y y | d d m o n y y ***OR*** ○$_1$ Continuing |
| ○$_9$ Chlorpropamide | d d m o n y y | d d m o n y y ***OR*** ○$_1$ Continuing |
| ○$_{10}$ Cladribine | d d m o n y y | d d m o n y y ***OR*** ○$_1$ Continuing |

8

EPO-IMU-001_LOE-2_(28NOV2011).fm

**Janssen Research & Development, LLC**

**Global Medical Safety**

Protocol EPO-IMU-001

| GLOBAL AE #: |
|---|
| |

**MEDICATIONS from question #13 continued....**

*Fill in all that apply. If circle filled in, provide treatment medication start date information. If continuing, fill in circle. If treatment medication stopped, fill in stop date.*

| MEDICATIONS | START DATE | STOP DATE |
|---|---|---|
| ○ 12 D-Penicillamine | d d m o n y y | d d m o n y y **OR** ○ 1 Continuing |
| ○ 13 Dapsone | d d m o n y y | d d m o n y y **OR** ○ 1 Continuing |
| ○ 14 Diphenylhydantoin (phenytoin) | d d m o n y y | d d m o n y y **OR** ○ 1 Continuing |
| ○ 15 Fenoprofen | d d m o n y y | d d m o n y y **OR** ○ 1 Continuing |
| ○ 16 Gold | d d m o n y y | d d m o n y y **OR** ○ 1 Continuing |
| ○ 17 Indomethacin | d d m o n y y | d d m o n y y **OR** ○ 1 Continuing |
| ○ 18 Interferon | d d m o n y y | d d m o n y y **OR** ○ 1 Continuing |
| ○ 19 Isoniazid | d d m o n y y | d d m o n y y **OR** ○ 1 Continuing |
| ○ 20 Lamivudine | d d m o n y y | d d m o n y y **OR** ○ 1 Continuing |
| ○ 21 Lindane | d d m o n y y | d d m o n y y **OR** ○ 1 Continuing |
| ○ 36 Linezolid | d d m o n y y | d d m o n y y **OR** ○ 1 Continuing |
| ○ 22 Leuprolide | d d m o n y y | d d m o n y y **OR** ○ 1 Continuing |

**Janssen Research & Development, LLC**

**Global Medical Safety**

Protocol EPO-IMU-001

| GLOBAL AE #: |
|---|
| |

**MEDICATIONS from question #13 continued....**

*Fill in all that apply. If circle filled in, provide treatment medication start date information. If continuing, fill in circle. If treatment medication stopped, fill in stop date.*

| MEDICATIONS | START DATE | STOP DATE |
|---|---|---|
| ○23 Methazolamide | d d m o n y y | d d m o n y y **OR** ○1 Continuing |
| ○37 Mycophenolic Mophetil | d d m o n y y | d d m o n y y **OR** ○1 Continuing |
| ○24 Pentachlorophenol | d d m o n y y | d d m o n y y **OR** ○1 Continuing |
| ○25 Phenytoin | d d m o n y y | d d m o n y y **OR** ○1 Continuing |
| ○26 Procainamide | d d m o n y y | d d m o n y y **OR** ○1 Continuing |
| ○38 Ribavirin | d d m o n y y | d d m o n y y **OR** ○1 Continuing |
| ○27 Rifampin | d d m o n y y | d d m o n y y **OR** ○1 Continuing |
| ○28 Rituximab | d d m o n y y | d d m o n y y **OR** ○1 Continuing |
| ○39 Sulfamethoxazole | d d m o n y y | d d m o n y y **OR** ○1 Continuing |
| ○29 Sulfasalazine | d d m o n y y | d d m o n y y **OR** ○1 Continuing |
| ○30 Sulfobromopthalein sodium (bromsulphthalein) | d d m o n y y | d d m o n y y **OR** ○1 Continuing |
| ○40 Trimetoprim | d d m o n y y | d d m o n y y **OR** ○1 Continuing |

10

EPO-IMU-001_LOE-2_(28NOV2011).fm

**Janssen Research & Development, LLC**

**Global Medical Safety**

Protocol EPO-IMU-001

| GLOBAL AE #: |
|---|
| |

**MEDICATIONS from question #13 continued....**

*Fill in all that apply. If circle filled in, provide treatment medication start date information. If continuing, fill in circle. If treatment medication stopped, fill in stop date.*

| MEDICATIONS | START DATE | STOP DATE |
|---|---|---|
| ○ 31 Tacrolimus | d d m o n y y | d d m o n y y **OR** ○ 1 Continuing |
| ○ 32 Thiamphenicol | d d m o n y y | d d m o n y y **OR** ○ 1 Continuing |
| ○ 33 Valproic acid | d d m o n y y | d d m o n y y **OR** ○ 1 Continuing |
| ○ 34 Zidovudine | d d m o n y y | d d m o n y y **OR** ○ 1 Continuing |
| ○ 99 Other: _____ | d d m o n y y | d d m o n y y **OR** ○ 1 Continuing |

**14. Was immunosuppressive or other therapy used if and when PRCA was suspected and/or antibodies were suspected or confirmed?** ○ 2 Yes* ○ 1 No ○ 98 Unknown

**If Yes, please provide information below.*

| Immuno/therapy | Response to Immunotherapy | Start Date | Stop Date |
|---|---|---|---|
| 101. _____ _____ | ○ 1 Worse ○ 2 No change ○ 3 Improved ○ 4 Recovered | d d m o n y y | d d m o n y y **OR** ○ 98 Unknown |
| 102. _____ _____ | ○ 1 Worse ○ 2 No change ○ 3 Improved ○ 4 Recovered | d d m o n y y | d d m o n y y **OR** ○ 98 Unknown |
| 103. _____ _____ | ○ 1 Worse ○ 2 No change ○ 3 Improved ○ 4 Recovered | d d m o n y y | d d m o n y y **OR** ○ 98 Unknown |

11

EPO-IMU-001_LOE-2_(28NOV2011).fm

**Janssen Research & Development, LLC**

**Global Medical Safety**

Protocol EPO-IMU-001

| GLOBAL AE #: |
|---|
| ☐☐☐☐☐☐☐☐☐☐☐ |

15. Do you have any samples of the patient's serum prior to LOE available?

$O_2$ Yes $O_1$ No $O_{98}$ Unknown

If yes to above question , would these samples be available to Johnson & Johnson Pharmaceutical Research & Development, L.L.C. for antibody and epoetin level analysis?

$O_2$ Yes $O_1$ No $O_{98}$ Unknown

16. Was the patient transfusion dependent during period of LOE?

$O_2$ Yes $O_1$ No $O_{98}$ Unknown

17. Is the patient currently transfusion dependent? $O_2$ Yes $O_1$ No $O_{98}$ Unknown

If patient is not currently transfusion dependent, for how many months was the patient transfusion dependent after onset of LOE? ..... ☐☐ months

## FOLLOW-UP INFORMATION

YOUR CONTACT INFORMATION FOR FOLLOW-UP ISSUES:

Name: _____

Address: _____

Phone: _____ FAX: _____

Email: _____

*END OF QUESTIONNAIRE - THANK YOU*

*NOTE: If more space is needed to list lab results, please list results on separate page (with same format) and return page with questionnaire.*

12

EPO-IMU-001_LOE-2_(28NOV2011).fm

Janssen Research & Development, LLC
Global Medical Safety

**PRCA FOLLOW-UP QUESTIONNAIRE**
Bone Marrow and/or EPO Antibody Positive Patients

**Patient Identifiers: AE #:** _____
**Patient Initials:** _____ **Date of Birth:** _____
**Patient Gender:** _____ **Patient Race:** _____

## 1. Current Patient Status

| | |
|---|---|
| ☐ Died: Date of Death (day/month/year): _____/_____/_____<br>Cause of Death: _____ | |
| ☐ Alive: (Current PRCA Status is): ☐ Recovered/Resolved ☐ Improved ☐ Worsened ☐ No change | |
| Transfusion Requirements after diagnosis of PRCA: | ☐ Never Transfusion Dependent<br>☐ Anemia (episodic transfusions required)<br>☐ Transfusion Dependent (Frequency:_____ Units/Month)<br><br>Date of last transfusion after PRCA diagnosis (month/year): _____/_____ |

## 2. Epoetin Therapy Since PRCA Diagnosis

| | |
|---|---|
| A. Epoetin therapy stopped upon PRCA diagnosis? | ☐ Yes (go to Question B.) ☐ No (go to Question C.) |
| B. If "Yes" to Question A: Was Epoetin therapy restarted (re-challenge) after PRCA diagnosis? | ☐ Yes (go to Question C.) ☐ No (go to Section 3.) |
| C. If Epoetin therapy was restarted or continued after PRCA diagnosis, specify the following for that restarted /continued treatment: | Epoetin Brand: _____<br>Dose (IU)/Frequency: _____<br>Route: ☐ SC ☐ IV ☐ Both SC & IV<br>Date restarted (Month/Year): _____/_____<br>Ongoing? ☐ Yes or<br>☐ Discontinued:(Month/Year):<br>_____/_____ |

## 3. Treatment for PRCA Since PRCA Diagnosis

| | |
|---|---|
| PRCA Treatment | ☐ Yes ☐ No |
| If immunosuppressive or other treatment was administered for PRCA, please provide the following treatment details: | Therapy (drug name): 1) _____<br>2)_____<br><br>Dose/Frequency/Route: 1)_____<br>2)_____<br><br>Dates of therapy (Month/Year): 1) From _____/_____ To _____/_____<br>2) From _____/_____ To _____/_____ |
| Response to Therapy: | ☐ Recovered/Resolved ☐ Improved ☐ Worsened ☐ No change |

**Additional information/comments:** _____
_____
_____

**Name of person completing form:** _____ **Title:** _____
**Date (Day/Month/Year):** _____/_____/_____

*Please attach additional new information such as HLA Typing, bone marrow biopsy reports, hemoglobin levels, reticulocyte counts or new erythropoietin antibody testing results.*

## Annex 5: Protocols for Proposed and Ongoing Studies in RMP Part IV

Not applicable

## Annex 6: Details of Proposed Additional Risk Minimisation Activities (if applicable)

Not applicable

# Annex 7: Other Supporting Data (including referenced material)

## Annex 7.1 References

### Annex 7.1.1 Key References

None

### Annex 7.1.2 Other References

Aapro M, Jelkmann W, Constantinescu SN and Leyland-Jones B. Effects of erythropoietin receptors and erythropoiesis-stimulating agents on disease progression in cancer. British Journal of Cancer. 2012;106(7): 1249-1258.

Abraham PA. Practical approach to initiation of recombinant human erythropoietin therapy and prevention and management of adverse effects. Am J Nephrol. 1990;10(Suppl 2):7-14.

ADR Report. Analysis of adverse drug reaction terms from epoetinum alfa clinical studies within the oncology (chemotherapy induced anemia), chronic renal failure (dialysis and not on dialysis), autologous blood donation, perisurgery, and zidovudine-treated human immunodeficiency virus indications. Document Number EDMS-DEC-13294782:3.0. Janssen Research & Development (8 September 2010).

Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol. 2001;38(4):955-962.

American Cancer Society. Anemia in people with cancer. http://www.cancer.org/treatment/treatmentsandsideeffects/physicalsideeffects/anemia/anemia-in-people-with-cancer. Accessed 1 November 2015.

Aranesp [SMPC]. Breda, Netherlands: Amgen Europe B.V.; 2013.

Ardissino G, Daccò V, Testa S, et al. Epidemiology of chronic renal failure in children: data from the ItalKid project. Pediatrics. 2003;111(4 Pt 1): e382-e387.

Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). Arch Intern Med. 2002;162(12):1401-1408.

Astor BC, Coresh J, Heiss G, Pettitt D, Sarnak MJ. Kidney function and anemia as risk factors for coronary heart disease and mortality: the Atherosclerosis Risk in Communities (ARIC) Trial. Am Heart J. 2006;151(2):492-500.

Ayav, C, Beuscart JB, Briancon S. Competing risk of death and end-stage renal disease in incident chronic kidney disease (stages 3 to 5): the EPIRAN community-based study. BMC Nephrology 2016;7: 174.

Bennett CL, Cournoyer D, Carson KR, et al. Long-term outcome of individuals with pure red cell aplasia and antierythropoietin antibodies in patients treated with recombinant epoetin: a follow-up report from the Research on Adverse Drug Events and Reports (RADAR) Project. Blood. 2005;106:3343-3347.

Berstock JR, Beswick AD, Lenguerrand E, Whitehouse MR, Blom AW. Mortality after total hip replacement surgery: A systematic review. Bone Joint Res. 2014;3(6):175-182.

Besarab A, Bolton WK Browne J, Egrie J, Nissendon A, Okamoto D, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998;339:584-90.

Birgegård G, Aapro MS, Bokemeyer C, et al. Cancer-related anemia: pathogenesis, prevalence and treatment. Oncology. 2005;68(suppl 1):3-11.

Birgegård, G, Gascon P, Ludwig H. Evaluation of anaemia in patients with multiple myeloma and lymphoma: findings of the European CANCER ANAEMIA SURVEY. European Journal of Haematology 2006: 77(5): 378-386. http://dx.doi.org/10.1111/j.1600-0609.2006.00739.x.

Blohmer JU, Dunst J, Harrison L, Johnston P, Khayat D, Ludwig H, et al. (2005). "Cancer-related anemia: biological findings, clinical implications and impact on quality of life." Oncology. 2005:68 Suppl 1: 12-21.

Bou Monsef J, Figgie MP, Mayman D, Boettner F. Targeted pre-operative autologous blood donation: a prospective study of two thousand and three hundred and fifty total hip arthroplasties. Int Orthop. 2014;38(8): 1591-1595.

Boven K, Stryker S, Knight J, et al. The increased incidence of pure red cell aplasia with an EPREX formulation in uncoated rubber stopper syringes. Kidney Int. 2005; 67(6):2346-2353.

Bruck K, Stel VS, Gambaro G, et al. CKD Prevalence Varies across the European General Population. J Am Soc Nephrol. 2016;27(7): 2135-2147. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4926978/

Caro JJ, Salas M, Ward A, Goss G. Anemia as an independent prognostic factor for survival in patients with cancer: a systematic, quantitative review. Cancer. 2001;91(12):2214-2221.

Casadevall N, Eckardt KU, Rossert J. Epoetin-induced autoimmune pure red cell aplasia. J Am Soc Nephrol. 2005;16(Suppl 1):S67-S69.

CDC. National chronic kidney disease fact sheet 2010. http://www.cdc.gov/diabetes/pubs/factsheets/kidney.htm. 2010. Accessed 10 December 2013.

Cepoi V, Onofriescu M, Segall L, Covic A. The prevalence of chronic kidney disease in the general population in Romania: a study on 60,000 persons. Int Urol Nephrol. 2012;44(1): 213-220.

Chesnaye N, Bonthuis M, Schaefer F, et al. Demographics of paediatric renal replacement therapy in Europe: a report of the ESPN/ERA-EDTA registry. Pediatr Nephrol. 2014;29(12):2403-2410.

Collins AJ. Cardiovascular mortality in end-stage renal disease. Am J Med Sci. 2003;325(4):163-167.

Culliford D, Maskell J, Judge A, et al. Future projections of total hip and knee arthroplasty in the UK: results from the UK Clinical Practice Research Datalink. Osteoarthritis Cartilage. 2015;23(4):
594-600.

De Nicola L, Donfrancesco C, Minutolo R, et al. Prevalence and cardiovascular risk profile of chronic kidney disease in Italy: results of the 2008-12 National Health Examination Survey. Nephrol Dial Transplantation. 2015;30(5):806-814.

Dicato M, Plawny L, Diederich M. Anemia in cancer. Ann Oncol. 2010;21(Suppl 7):vii167-vii72.

Dinmohamed AG, Visser O, van Norden Y, et al, . Trends in incidence, initial treatment and survival of myelodysplastic syndromes: a population-based study of 5144 patients diagnosed in the Netherlands from 2001 to 2010. Eur J Cancer. 2014;50(5):1004-1012.

Drueke TB, Locatelli F, Clyne N, Edkardt KU, Macdougall IC, Tsakins D, et al. Normalization of hemoglobin level in patients with chronic kidney disease. N Engl J Med. 2006;355:2071-84.

Eckardt KU, Casadevall N. Pure red cell aplasia due to anti-erythropoietin antibodies. Nephrol Dial Transplant. 2003;18(5):865-869.

Fenaux P (2014), Haase D, Sanz GF, Santini V, Buske C. Myelodysplastic syndromes: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(Suppl 3):iii57-iii69.

Ferris ME (2006), Gipson DS, Kimmel PL, Eggers PW. Trends in treatment and outcomes of survival of adolescents initiating end-stage renal disease care in the United States of America. Pediatr Nephrol. 2006;21(7):1020-1026.

Gascon P and Barrett-Lee PJ. Prevalence of anemia in cancer patients not receiving antineoplastic treatment (ANT): Data from the European Cancer Anaemia Survey (ECAS). Journal of Clinical Oncology 2006;24(18_suppl): 8565-8565. http://ascopubs.org/doi/abs/10.1200/jco.2006.24.18_suppl.8565

Gombotz, H, Rehak PH, Shander A, Hofmann A. The second Austrian benchmark study for blood use in elective surgery: results and practice change. Transfusion. 2014;54(10 Pt 2): 2646-2657.

Goodnough LT. Autologous blood donation. Crit Care. 2004;8(Suppl 2):S49-S52.

Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. Pediatr Nephrol. 2012;27(3):363-373.

Haematological Malignancy Research Network (HMRN). Prevalence: Myelodysplastic Syndroms. https://www.hmrn.org/statistics/prevalence. Accessed 19 Dec 2017.

Jameson K, Jick S, Hagberg KW, Ambegaonkar N, Giles A, O'Donoghue D. Prevalence and management of chronic kidney disease in primary care patients in the UK. Int J Clin Pract. 2014;68(9):1110-1121.

Jans Ø, Jørgensen C, Kehlet H, Johansson PI, for the Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group. Role of preoperative anemia for risk of transfusion and postoperative morbidity in fast-track hip and knee arthroplasty. Transfusion. 2014;54(3): 717-726.

Jans Ø, Bandholm T, Kurbegovic S, et al. Postoperative anemia and early functional outcomes after fast-track hip arthroplasty: a prospective cohort study. Transfusion. 2016;56(4):917-925.

Kazmi WH (2001), Kausz AT. Khan S, et al. Anemia: an early complication of chronic renal insufficiency. Am J Kidney Dis. 2001;38(4):803-812.

Kellokumpu-Lehtinen PL, Puistola U, Paija O, et al. Anaemia: a rare but neglected problem among Finnish patients receiving chemotherapy for solid tumours. Support Care Cancer. 2011;19(1): 149-153.

Kerr M, Bray B, Medcalf J, O'Donoghue DJ, Matthews B. Estimating the financial cost of chronic kidney disease to the NHS in England. Nephrol Dial Transplant. 2012;27(Suppl 3):iii73-iii80.

Knight K, Wade S, Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. Am J Med. 2004;116(Suppl 7A):11S-26S.

Koshy SM, Geary DF. Anemia in children with chronic kidney disease. Pediatr Nephrol. 2008;23(2):209-219.

Kosmidis P, Krzakowski M, ECAS Investigators. Anemia profiles in patients with lung cancer: what have we learned from the European Cancer Anemia Survey (ECAS)? Lung Cancer. 2005;50(3): 401-412.

Krischock LA, van Stralen KJ, Verrina E, et al. Anemia in children following renal transplantation-results from the ESPN/ERA-EDTA Registry. Pediatr Nephrol 2016;31(2): 325-333.

Kuznik A, Mardekian J, Tarasenko L. Evaluation of cardiovascular disease burden and therapeutic goal attainment in US adults with chronic kidney disease: an analysis of national health and nutritional examination survey data, 2001-2010. BMC Nephrol. 2013;14: 132.

Landray MJ, Emberson JR, Blackwell L. Prediction of ESRD and death among people with CKD: the chronic renal impairment in Birmingham (CRIB) prospective cohort study. Am J Kidney Dis. 2010;56(6):1082-1094.

Li J. Myelodysplastic syndrome hematopoietic stem cell. Int J Cancer, 2013;133(3): 525-533.

Link H and Schmitz S. Treatment of cancer-associated anaemia: results from a two-day cross-sectional survey in Germany. Onkologie 2013;36(5): 266-272.

Löfvendahl S, Bizjajeva S, Ranstam J, Lidgren L. Indications for hip and knee replacement in Sweden. J Eval Clin Pract. 2011;17(2): 251-260.

Ludwig H, Van Belle S, Barrett-Lee P, et al. The European cancer anaemia survey (ECAS): a large, multinational, prospective trial defining the prevalence, incidence, and treatment of anaemia in cancer patients. Eur J Cancer. 2004;40:2293-2306.

Macdougall IC. Antibody-mediated pure red cell aplasia (PRCA): epidemiology, immunogenicity and risks. Nephrol Dial Transplant. 2005;20(Supp 4):iv9-iv15.

Macdougall IC, Roger SD, de Francisco A, et al. Antibody-mediated pure red cell aplasia in chronic kidney disease patients receiving erythropoiesis-stimulating agents: new insights. Kidney Int. 2012;81(8):727–732.

Martin K (2010), Keller E, Gertler R et al. Efficiency and safety of preoperative autologous blood donation in cardiac surgery: a matched-pair analysis in 432 patients. Eur J Cardio-thoracic Surg. 2010;37(6):1396-1401.

Maynadié M, De Angelis R, Marcos-Gragera R, et al, for the HAEMACARE Working Group. Survival of European patients diagnosed with myeloid malignancies: a HAEMACARE study. Haematologica. 2013;98(2):230-238.

Mayo Clinic. Knee replacement. http://www.mayoclinic.com/health/knee-replacement/MY00091. 2013. Accessed 5 December 2013.

Mayo Clinic. Chronic kidney failure: treatments and drugs. http://www.mayoclinic.com/ diseases-conditions/kidney-disease/basics/treatment/con-20026778. 2015. Accessed 30 October 2015.

McClellan WM, Flanders WD, Langston RD, Jurkovitz C, Presley R. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based trial. J Am Soc Nephrol. 2002;13(7):1928-1936.

McClellan W, Aronoff SL, Bolton WK, Hood S, Lorber DL, Tang KL, et al. The Prevalence of anemia in patients with chronic kidney disease. Curr Res Opin 2004;20(9):1501-10.

Menendez ME and D. Ring D. Minorities are less likely to receive autologous blood transfusion for major elective orthopaedic surgery. Clin Orthop Relat Res 2014;472(11): 3559-3566. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4182418/

Nakamura Y, Tsuchiya K, Nitta K, Ando M. Prevalence of anemia and chronic kidney disease in cancer patients: clinical significance for 1-year mortality. Nihon Jinzo Gakkai Shi. 2011;53(1):38-45.

NeoRecormon [SMPC]. Welwyn Garden City, United Kingdom: Roche Registration Limited; 2012.

National Institute of Diabetes and Digestive and Kidney Diseases. (2014a, July 2014). Anemia in Chronic Kidney Disease. Retrieved Feb. 15, 2018, from https://www.niddk.nih.gov/health-information/kidney-disease/chronic-kidney-disease-ckd/anemia.

National Institute of Diabetes and Digestive and Kidney Diseases. (2014b, March 2014). Kidney Disease in Children. Retrieved Feb. 15, 2018, from https://www.niddk.nih.gov/health-information/kidney-disease/children.

NIH Consensus Panel. NIH Consensus Statement on total knee replacement December 8-10, 2003. J Bone Joint Surg Am. 2004;86-A (6):1328-1335.

NKDEP. Health professionals: chronic kidney disease information. www.niddk.nih.gov/health-information/healthcare-professionals/pages/default.aspx. 2011. Accessed 30 October 2015.

ODAC Background (2007a). Benefits and Risks of Erythropoiesis Stimulating Agents (ESAs) for the Treatment of Chemotherapy-Induced Anemia. Information for Oncologic Drugs Advisory Committee Meeting 10 May 2007. EDMS-USRA-10308479:2.0. J&JPRD (6 Apr 2007).

ODAC (2007b). Supplement to background information for the oncologic drugs advisory committee 10 May 2007. ttp://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4301b2-01-01-AMGEN-odac-supplement-2007.pdf. 2007. Accessed 9 April 2009.

ODAC (2007c). Briefing information for the oncologic drugs advisory committee 10 May 2007. http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4301b2-00-index.htm. 2007. Accessed 5 February 2009.

OECD/EU. Hip and knee replacement. Health at a Glance: Europe 2016: State of Health in the EU Cycle. Paris, OECD Publishing.

Orphanet. Prevalence and incidence of rare diseases: bibliographic data. Orphanet Report Series: Rare Diseases collection.2015; Number 1. http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf. Accessed 24 June 2015.

Orphanet. Orphanet Report Series - Prevalence of rare diseases: Bibliographic data - June 2017. Orphanet Report Series. 2017 Haematological Malignancy Research Network (HMRN). https://www.hmrn.org/statistics. Accessed 19 December 2017.

Penninx BW, Cohen WJ, Woodman RC. Anemia and cancer in older persons. J Support Oncol. 2007;5(3):107-113.

Pfeffer MA, Burdmann EA, Chen CY, Cooper M, Zeeuw D, Eckardt K, et al. A trial of darbepoetin alfa in Type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361(21):2019-2032.

Politis C, Richardson SC. An update on predeposit autologous blood donation and transfusion in Europe. Vox Sang. 2004;87:105-108.

Preston NJ, Hurlow A, Brine J, Bennett MI. Blood transfusions for anaemia in patients with advanced cancer. Cochrane Database Syst Rev. 2012;2:CD009007.

Ryan MH, Heavner GA, Brigham-Burke M, et al. An in vivo model to assess factors that may stimulate the generation of an immune reaction to erythropoietin. Int Immunopharmacol. 2006;6(4):647-655.

Sant, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood. 2010;116(19):3724-3734.

Saran, R, Li Y, Robinson B, Ayanian J, et al. US Renal Data System 2014 Annual Data Report: Epidemiology of Kidney Disease in the United States Vol 2. Am J Kidney Dis. 2015;66(1 Suppl 1):Svii, S1-S305.

Schellekens H (2006), Jiskoot W. Erythropoietin-associated PRCA: still an unsolved mystery. J Immunotoxicol. 2006;3(3):123-130.

Semiannual immunogenicity report: erythropoietin antibody-positive pure red cell aplasia with data through 30 June 2015. Document Number: EDMS-ERI-110144622. Janssen Research & Development (14 Aug 2015).

Singh A, Szczech L, Tang K, Barnhart H, Sapp S, Wolfson M, et al. Correction of anemia with epoetin alfa in chronic kidney disease (CHOIR trial). N Engl J Med 2006;355:2085-2098.

Singh JA. Epidemiology of knee and hip arthroplasty: a systematic review. Open Orthop J. 2011;5:80-85.

Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. Anesthesiol. 2010;113(2):482-495.

Staples AO, Wong CS, Smith JM, et al. Anemia and risk of hospitalization in pediatric chronic kidney disease. Clin J Am Soc Nephrol. 2009;4(1):48-56.

Stauffer ME and Fan T. Prevalence of Anemia in Chronic Kidney Disease in the United States. 2014: PLoS ONE 9(1): e84943. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3879360/

Steegmann JL, Sanchez Torres JM, Colomer R. Prevalence and management of anaemia in patients with non-myeloid cancer undergoing systemic therapy: a Spanish survey. Clin Transl Oncol 2013;15(6): 477-483. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3663988/

Stringer S, Sharma P, Dutton M, Jesky M, Ng K, Kaur O, et al. The natural history of, and risk factors for, progressive Chronic Kidney Disease (CKD): the Renal Impairment in Secondary care (RIISC) study; rationale and protocol. BMC Nephrology 2013;14(1): 95.

Swedberg K, Young J, Anand I, Cheng S, Desai A, Diaz R, et al. Treatment of anemia with darbepoetin alfa in systolic heart failure (RED-HF). N Engl J Med 2013;368:1210-1219.

Tehrani F, Dhesi P, Daneshvar D, Phan A, Rafique A, Siegel R, et al. Erythropoiesis stimulating agents in heart failure patients with anemia: a meta-analysis. Cardiovasc Drugs Ther. 2009;23:511–518.

Thorp ML, Johnson ES, Yang X, Petrick AF, Platt R, Smith DH. Effect of anaemia on mortality, cardiovascular hospitalizations and end-stage renal disease among patients with chronic kidney disease. Nephrol. 2009;14:240-246.

Tsai WC, Wu, HY, Peng YS. Risk Factors for Development and Progression of Chronic Kidney Disease: A Systematic Review and Exploratory Meta-Analysis. Medicine (Baltimore) 2016: 95(11): e3013. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4839895/

United States Renal Data System (USRDS) 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Bethesda, MD, USA, 2010. http://www.usrds.org/adr.htm. Accessed July 2010.

United States Renal Data System (USRDS). 2017 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2017. https://www.usrds.org/adr.aspx.

Van Beers MM, Jiskoot W, Schellekens H. On the role of aggregates in the immunogenicity of recombinant human interferon beta in patients with multiple sclerosis. J Interferon Cytokine Res. 2010;30:767-775.

Vinhas J, Gardete-Correia L, Boavida JM, et al. Prevalence of chronic kidney disease and associated risk factors, and risk of end-stage renal disease: data from the PREVADIAB study. Nephron Clin Pract. 2011;119(1): c35-c40.

Zhan C, Kaczmarek R, Loyo-Berrios N, Sangl J, Bright RA. Incidence and short-term outcomes of primary and revision hip replacement in the United States. J Bone Joint Surg Am. 2007;89(3):526-533.

Zoccali C, Kramer A, Jager KJ. Chronic kidney disease and end-stage renal disease—a review produced to contribute to the report ‘the status of health in the European union: towards a healthier Europe’. NDT Plus. 2009;3:213–224.

## Annex 7.2 Abbreviations

| | |
|---|---|
| Ab | antibody |
| ABD | autologous blood donation |
| ACE | angiotensin-converting enzyme |
| ADR | adverse drug reaction |
| ALT | alanine aminotransferase |
| AML | acute myelogenous leukaemia |
| ANSM | L'Agence Nationale de Sécurité du Médicament et des Produits de Santé |
| AST | aspartate aminotransferase |
| BMI | body mass index |
| BSA | body surface area |
| CHF | congestive heart failure |
| CHMP | Committee for Medicinal Products for Human Use |
| CHOIR | Correction of Haemoglobin and Outcomes in Renal Insufficiency, Trial PR00-06-014 |
| CI | confidence interval |
| CIA | chemotherapy-induced anaemia |
| CKD | chronic kidney disease |
| CRCL/CrCl | creatinine clearance |
| CRF | chronic renal failure |
| CSR | clinical study report |
| CV | cardiovascular |
| CVD | cardiovascular disease |
| DVT | deep vein thrombosis |
| ECAS | European Cancer Anaemia Survey |
| EDTA | European Dialysis and Transplantation Association |
| EEA | European Economic Area |
| eGFR | estimated glomerular filtration rate |
| ERA | European Renal Association |
| ESA | erythropoiesis-stimulating agent |
| ESRD | end-stage renal disease |
| EU | European Union |
| GFR | glomerular filtration rate |
| Hct | haematocrit |
| HGB | haemoglobin |
| HIV | human immunodeficiency virus |
| HMRN | Haematological Malignancy Research Network |
| HR | hazard ratio |
| ICH | International Council for Harmonisation |
| Ig | immunoglobulin |
| IM | intramuscular |
| IMS | Intercontinental Medical Statistics |
| IMS MIDAS | Intercontinental Medical Statistics Multinational Integrated Data Analysis System |
| IPSS | International Prognostic Scoring System |
| IR | incidence rate |
| IU | international units |
| IV | intravenous |
| MAH | marketing authorisation holder |
| MDS | myelodysplastic syndrome |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | myocardial infarction |
| N/n | number |
| NAPRTCS | North American Pediatric Renal Trials and Collaborative Studies |
| NHANES | National Health and Nutrition Examination Survey |
| NHS | National Health Service |
| NKDEP | National Kidney Disease Education Program |
| NYHA | New York Heart Association |
| OA | osteoarthritis |

| | |
|---|---|
| OR | odds ratio |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PFS | progression-free survival |
| PHR | partial hip replacement |
| pmarp | per million of the age-related population |
| PRCA | pure red cell aplasia |
| PS-80 | polysorbate-80 |
| PSUR | Periodic Safety Update Report |
| PY | person years |
| Q2W | once every 2 weeks |
| Q3W | once every 3 weeks |
| Q4W | once every 4 weeks |
| QD | once daily |
| QW | once weekly |
| RBC | red blood cell |
| RMP | risk management plan |
| RR | relative risk |
| RRT | renal replacement therapy |
| Rx | prescriptions |
| SBP | systolic blood pressure |
| SC | subcutaneous |
| SmPC | Summary of Product Characteristics |
| SMQ | standard MedDRA query |
| THR | total hip replacement |
| TIW | 3 times per week |
| TKR | total knee replacement |
| TVE | thrombotic vascular event |
| UK | United Kingdom |
| ULN | upper limit of normal |
| US | United States |
| USRDS | United States Renal Data System |

## Annex 8: Summary of Changes to the Risk Management Plan Over Time

| Version | Approval Date<br>Procedure | Change |
|---|---|---|
| 1.0 | 08 Dec 2004 | 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 | New risk identified. |
| 3.0 | 24 Sep 2010 | Trial Completion: Trials EPO-AKD-3001, EPO-AKD-3002, EPOANE4008, and EPO-CKD-2002. Adverse drug reaction risks were identified but no new ones were considered as important for RMP purposes. |
| 4.0 | 26 Oct 2011 | New template |
| 5.0 | 04 Mar 2016 | New template; new indication: MDS; Trial completion: EPOANE4076 |
| 5.4 | 28 Jun 2018<br>FR/H/0003/009-010, 013-014/II/129 | Draft versions:<br>5.1: Added new important potential risks: Seizures and Hypersensitivity/Anaphylaxis; updated important identified risk of Hypertension to Hypertension/Hypertensive crisis<br>5.3: Risks of Seizures and Hypersensitivity/Anaphylaxis moved from important potential risks to important identified risks.<br><br>Outcome:<br>- Updated important identified risk of Hypertension to Hypertension/Hypertensive crisis.<br>- Seizures and Hypersensitivity/Anaphylaxis were not maintained as important identified risks. |
| 6.0 Succession 1 | Current procedure<br>FR/H/0003/009-010, 013-014/II/132 | Draft versions:<br><br>5.2: Updated with data from CSR EPOANE 3010 and additional subjects from the CSR EPOANE 3021 extension. Study EPOANE 3010 compared treatment with epoetin alfa plus standard supportive care with standard supportive care only in aaemic patients with metastatic breast cancer receiving standard chemotherapy. Trial EPOANE 3021 was conducted to demonstrate the effectiveness of epoetin alfa in inducing and maintaining erythroid response,<br>significantly reducing the percentage of patients requiring transfusion, and prolonging the time to |

| Version | Approval Date<br>Procedure | Change |
|---|---|---|
| | | first RBC transfusion in patients with IPSS low- or intermediate-1 risk MDS.<br><br>6.0 Succession 1:<br>Updated to remove Thrombotic vascular events and Hypertension/Hypertensive crisis as important identified risks and to remove CHF as an important potential risk. These risks have been removed to align the safety concerns with the GVP Module V (rev 2).<br>Updated to align with the outcome of procedure FR/H/003/09-10, 13-14/II/129 (approved RMP Version 5.4) and to modify the objectives of the annual immunogenicity reports. |