

**European Union Risk Management Plan**  
**EPREX<sup>®</sup> (epoetin alfa)**

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Data lock point for current RMP

31 August 2021

Version number

7.2

Final for Procedure FR/H/xxxx/WS/282 - Health Authority approval date 10 October 2022

**QPPV Sign-off Date:** 17 October 2022  
**RMP Version Number:** 7.2  
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**Confidentiality Statement**

The information provided herein contains Company trade secrets, commercial or financial information that the Company customarily holds close and treats as confidential. The information is being provided under the assurance that the recipient will maintain the confidentiality of the information under applicable statutes, regulations, rules, protective orders or otherwise.

Qualified Person for Pharmacovigilance (QPPV) Name(s): [REDACTED], PharmD, PhD

QPPV Signature: The Marketing Authorization Holder (MAH) QPPV has either reviewed and approved this Risk Management Plan (RMP), or approved with an electronic signature appended to this RMP, as applicable.

<b>Details of this RMP Submission</b>	
Version Number	7.2
Rationale for submitting an updated RMP	<p>Implementation of the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) conclusions regarding the assessment of the 17th and 18th immunogenicity reports (second and third annual reports, respectively), namely removal of annual immunogenicity reports and Independent Safety Advisory Committee (ISAC) adjudication from the list of routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.</p> <p>Implementation of minor changes requested by ANSM further to the review of EU-RMP Version 7.1, namely clarification that the second and third annual immunogenicity reports were the 17th and 18th reports overall, clarification that a statement on comorbidities in pediatric patients was specific to pediatric patients with chronic renal failure (CRF), and correction of a formatting error in Part VI.II.B.</p>

<b>Details of this RMP Submission</b>	
Summary of significant changes in this RMP	<p><u>Part I:</u></p> <ul style="list-style-type: none"> <li>Removal of Bulgaria, Finland, Ireland, and Norway from the list of MAHs (EPREX/ERYPO licenses withdrawn).</li> </ul> <p><u>Part II Module SI.1</u></p> <ul style="list-style-type: none"> <li>Addition of ‘CRF’ to clarify that comorbidities in the pediatric population relate specifically to pediatric patients with CRF.</li> </ul> <p><u>Part II Module SV:</u></p> <ul style="list-style-type: none"> <li>Update of postmarketing exposure data to align with the most recent Periodic Benefit-Risk Evaluation Report (PBRER) (data lock point 31 August 2021).</li> </ul> <p><u>Part III:</u></p> <ul style="list-style-type: none"> <li>Removal of annual immunogenicity reports and ISAC adjudication from the list of routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.</li> </ul> <p>Editorial changes made throughout to align with the latest company RMP template and the approved European Union (EU)-Mutual Recognition Procedure (MRP) Product Information.</p> <p>Formatting changes made to the Table in Part VI.II.B.</p>

**Other RMP Versions Under Evaluation:**

<b>RMP Version Number</b>	<b>Submitted on</b>	<b>Procedure Number</b>
None		

**Details of the Currently Approved RMP:**

Version number of last agreed RMP:	6.0 Succession 2
Approved within procedure	FR/H/0003/009-010, 013-014/II/132
Date of approval (MRP End of Procedure)	28 March 2019

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**PART I: PRODUCT(S) OVERVIEW**

<b>Active substance(s) (INN or common name)</b>	Epoetin alfa
<b>Pharmacotherapeutic group(s) (ATC Code)</b>	Other antianemic preparations B03XA01
<b>Marketing Authorization Holder</b>	Janssen-Cilag Pharma GmbH, Austria Janssen-Cilag NV, Belgium Janssen-Cilag International NV, Cyprus Janssen-Cilag s.r.o., Czech Republic Janssen-Cilag A/S, Denmark JANSSEN-CILAG, France JANSSEN-CILAG GmbH, Germany Janssen-Cilag Pharmaceutical S.A.C.I., Greece Janssen-Cilag SpA, Italy Janssen-Cilag, NV, Luxembourg Janssen-Cilag International NV, Malta Janssen-Cilag BV, Netherlands Janssen-Cilag Farmaceutica, Lda, Portugal Janssen-Cilag S.A., Romania Johnson & Johnson, Prodaja medicinskih in farmacevtskih izdelkov d.o.o., Slovenia Janssen-Cilag S.A., Spain Janssen-Cilag AB, Sweden Janssen-Cilag Ltd, United Kingdom
<b>Medicinal products to which the RMP refers</b>	1 (EPREX <sup>®</sup> /ERYPO <sup>®</sup> )
<b>Invented name(s) in the European Economic Area (EEA)</b>	EPREX <sup>®</sup> /ERYPO <sup>®</sup>
<b>Marketing authorization procedure</b>	Mutual recognition and National
<b>Brief description of the product</b>	<b>Chemical class</b> Erythropoietin is a mitosis-stimulating factor and differentiating hormone, which stimulates erythropoiesis.
	<b>Summary of mode of action</b> The efficacy of epoetin alfa has been demonstrated in humans in clinical trials and postauthorization use. After administration of epoetin alfa, the number of erythrocytes, hemoglobin (HGB) values, reticulocyte counts, and the iron-incorporation rate increase.
	<b>Important information about its composition</b> 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.
<b>Reference to the Product Information</b>	Module 1.3.1, Summary of Product Characteristics, Package Leaflet (PL)

<p><b>Indication(s) in the EEA</b></p>	<p><b>Current:</b></p> <p><b><u>Chronic renal failure</u></b></p> <p>EPREX, ERYPO is indicated for the treatment of symptomatic anaemia associated with chronic renal failure (CRF):</p> <ul style="list-style-type: none"> <li>• In adults and paediatrics aged 1 to 18 years on haemodialysis and adult patients on peritoneal dialysis.</li> <li>• In adults with renal insufficiency not yet undergoing dialysis for the treatment of severe anaemia of renal origin accompanied by clinical symptoms in patients.</li> </ul> <p><b><u>Cancer</u></b></p> <p>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.</p> <p><b><u>Autologous blood donation</u></b></p> <p>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).</p> <p><b><u>Surgery</u></b></p> <p>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).</p> <p><b><u>Treatment of adult patients with low- or intermediate-1-risk myelodysplastic syndromes</u></b></p> <p>EPREX, ERYPO is indicated for the treatment of symptomatic anaemia (HGB concentration of <math>\leq 10</math> g/dL) in adults with low- or intermediate-1-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin (<math>&lt; 200</math> mU/mL).</p>
	<p><b>Proposed:</b></p> <p>Not applicable</p>

<p><b>Dosage in the EEA</b></p>	<p><b>Current:</b></p> <p><b><u>Treatment of symptomatic anaemia in adult CRF patients</u></b></p> <p>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.</p> <p>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.</p> <p>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 10 g/dL (6.2 mmol/L) to 12 g/dL (7.5 mmol/L).</p> <p>A sustained HGB level of greater than 12 g/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 12 g/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.</p> <p>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).</p> <p>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.</p> <p>Treatment with EPREX, ERYPO is divided into 2 stages – correction and maintenance phase.</p> <p><b>Adult haemodialysis patients</b></p> <p>In patients on haemodialysis where intravenous (IV) access is readily available, administration by the IV route is preferable.</p> <p><b><u>Correction phase:</u></b></p> <p>The starting dose is 50 international units (IU)/kg, 3 times per week.</p> <p>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).</p>
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	<p><u>Maintenance phase:</u></p> <p>The recommended total weekly dose is between 75 IU/kg and 300 IU/kg.</p> <p>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).</p> <p>Patients with very low initial HGB (&lt;6 g/dL or &lt;3.75 mmol/L) may require higher maintenance doses than patients whose initial anaemia is less severe (&gt;8 g/dL or &gt;5 mmol/L).</p> <p><b>Adult patients with renal insufficiency not yet undergoing dialysis</b></p> <p>Where IV access is not readily available EPREX, ERYPO may be administered subcutaneously (SC).</p> <p><u>Correction phase:</u></p> <p>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).</p> <p><u>Maintenance phase:</u></p> <p>During the maintenance phase, EPREX, ERYPO can be administered either 3 times per week, and in the case of SC administration, once weekly (QW) or once every 2 weeks.</p> <p>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.</p> <p>The maximum dosage should not exceed 150 IU/kg 3 times per week, 240 IU/kg (up to a maximum of 20,000 IU) QW, or 480 IU/kg (up to a maximum of 40,000 IU), once every 2 weeks.</p> <p><b>Adult peritoneal dialysis patients</b></p> <p>Where IV access is not readily available, EPREX, ERYPO may be administered SC.</p> <p><u>Correction phase:</u></p> <p>The starting dose is 50 IU/kg, 2 times per week.</p> <p><u>Maintenance phase:</u></p> <p>The recommended maintenance dose is between 25 IU/kg and 50 IU/kg, 2 times per week in 2 equal injections.</p> <p>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).</p> <p><b><u>Treatment of adult patients with chemotherapy-induced anaemia</u></b></p> <p>Anaemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual</p>
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	<p>patient's clinical course and condition is necessary.</p> <p>EPREX, ERYPO should be administered to patients with anaemia (eg, HGB concentration <math>\leq 10</math> g/dL [6.2 mmol/L]).</p> <p>The initial dose is 150 IU/kg SC, 3 times per week.</p> <p>Alternatively, EPREX, ERYPO can be administered at an initial dose of 450 IU/kg SC QW.</p> <p>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).</p> <p>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 10 g/dL (6.2 mmol/L) to 12 g/dL (7.5 mmol/L). A sustained HGB concentration of greater than 12 g/dL (7.5 mmol/L) should be avoided; guidance for appropriate dose adjustment for when HGB concentrations exceed 12 g/dL (7.5 mmol/L) is described below.</p> <p>If the HGB concentration has increased by at least 1 g/dL (0.62 mmol/L) or the reticulocyte count has increased <math>\geq 40,000</math> cells/<math>\mu</math>L above baseline after 4 weeks of treatment, the dose should remain at 150 IU/kg 3 times per week or 450 IU/kg QW.</p> <p>If the HGB concentration increase is <math>&lt; 1</math> g/dL (<math>&lt; 0.62</math> mmol/L) and the reticulocyte count has increased <math>&lt; 40,000</math> cells/<math>\mu</math>L 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 <math>\geq 1</math> g/dL (<math>\geq 0.62</math> mmol/L) or the reticulocyte count has increased <math>\geq 40,000</math> cells/<math>\mu</math>L, the dose should remain at 300 IU/kg 3 times per week.</p> <p>If the HGB concentration has increased <math>&lt; 1</math> g/dL (<math>&lt; 0.62</math> mmol/L) and the reticulocyte count has increased <math>&lt; 40,000</math> cells/<math>\mu</math>L above baseline, response is unlikely and treatment should be discontinued.</p> <p><u>Dose adjustment to maintain HGB concentrations between 10 g/dL to 12 g/dL</u></p> <p>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%.</p> <p>If the HGB concentration level exceeds 13 g/dL (8.1 mmol/L), discontinue therapy until it falls below 12 g/dL (7.5 mmol/L) and then reinitiate EPREX, ERYPO therapy at a dose 25% below the previous dose.</p> <p>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.</p> <p>EPREX, ERYPO therapy should continue until 1 month after the</p>
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	<p>end of chemotherapy.</p> <p><b><u>Treatment of adult surgery patients in an autologous predonation programme</u></b></p> <p>Mildly anaemic patients (haematocrit [HCT] of 33% to 39%) requiring predeposit of <math>\geq 4</math> units of blood should be treated with EPREX, ERYPO 600 IU/kg IV, 2 times per week for 3 weeks prior to surgery. EPREX, ERYPO should be administered after the completion of the blood donation procedure.</p> <p><b><u>Treatment of adult patients scheduled for major elective orthopaedic surgery</u></b></p> <p>The recommended dose is EPREX, ERYPO 600 IU/kg administered SC weekly for 3 weeks (Days -21, -14, and -7) prior to surgery and on the day of surgery.</p> <p>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 SC daily for 10 consecutive days prior to surgery, on the day of surgery, and for 4 days immediately thereafter.</p> <p>If the HGB level reaches 15 g/dL, or higher, during the preoperative period, administration of EPREX, ERYPO should be stopped and further dosages should not be administered.</p> <p><b><u>Treatment of adult patients with low- or intermediate-1-risk MDS</u></b></p> <p>EPREX, ERYPO should be administered to patients with symptomatic anaemia (eg, HGB concentration <math>\leq 10</math> g/dL [6.2 mmol/L]).</p> <p>The recommended starting dose is EPREX, ERYPO 450 IU/kg (maximum total dose is 40,000 IU) administered SC once every week, with not less than 5 days between doses.</p> <p>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). It is recommended that initial erythroid response be assessed 8 to 12 weeks following initiation of treatment. Dose increases and decreases should be done one dosing step at a time. An HGB concentration of greater than 12 g/dL (7.5 mmol/L) should be avoided.</p> <p><b><u>Dose increase</u></b></p> <p>Dose should not be increased over the maximum of 1050 IU/kg (total dose 80,000 IU) per week. If the patient loses response or HGB concentration drops by <math>\geq 1</math> g/dL upon dose reduction, the dose should be increased by one dosing step. A minimum of 4 weeks should elapse between dose increases.</p> <p><b><u>Dose hold and decrease</u></b></p> <p>Epoetin alfa should be withheld when the HGB concentration exceeds 12 g/dL (7.5 mmol/L). Once the HGB level is <math>&lt; 11</math> g/dL the dose can be restarted on the same dosing step or one dosing step down based on physician judgement. Decreasing the dose by one</p>
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	<p>dosing step should be considered if there is a rapid increase in HGB (&gt;2 g/dL over 4 weeks).</p> <p>Anaemia symptoms and sequelae may vary with age, gender, and co-morbid medical conditions; a physician's evaluation of the individual patient's clinical course and condition is necessary.</p> <p><b><u>Paediatric population: treatment of symptomatic anaemia in chronic renal failure patients on haemodialysis</u></b></p> <p>Anaemia symptoms and sequelae may vary with age, gender, and co-morbid medical conditions; a physician's evaluation of the individual patient's clinical course and condition is necessary.</p> <p>In paediatric patients the recommended HGB concentration range is between 9.5 g/dL to 11 g/dL (5.9 to 6.8 mmol/L). EPREX, ERYPO should be administered in order to increase HGB to not greater than 11 g/dL (6.8 mmol/L). A rise in HGB of greater than 2 g/dL (1.25 mmol/L) over a 4-week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.</p> <p>Patients should be monitored closely to ensure that the lowest approved dose of EPREX, ERYPO is used to provide adequate control of anaemia and of the symptoms of anaemia.</p> <p>Treatment with EPREX, ERYPO is divided into 2 stages – correction and maintenance phase.</p> <p>In paediatric patients on haemodialysis where IV access is readily available, administration by the IV route is preferable.</p> <p><b><u>Correction phase</u></b></p> <p>The starting dose is 50 IU/kg IV, 3 times per week.</p> <p>If necessary, increase or decrease the dose by 25 IU/kg (3 times per week) until the desired HGB concentration range of between 9.5 g/dL to 11 g/dL (5.9 to 6.8 mmol/L) is achieved (this should be done in steps of at least 4 weeks).</p> <p><b><u>Maintenance phase</u></b></p> <p>Appropriate adjustment of the dose should be made in order to maintain HGB levels within the desired concentration range between 9.5 g/dL to 11 g/dL (5.9 to 6.8 mmol/L).</p> <p>Generally, children under 30 kg require higher maintenance doses than children over 30 kg and adults.</p> <p>Paediatric patients with very low initial HGB (&lt;6.8 g/dL or &lt;4.25 mmol/L) may require higher maintenance doses than patients whose initial HGB is higher (&gt;6.8 g/dL or &gt;4.25 mmol/L).</p>
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	<b>Proposed:</b> Not applicable	
<b>Pharmaceutical form(s) and strengths</b>	<b>Current:</b> Clear, colorless solution for injection in prefilled syringe in the following strengths: 2,000 IU/mL, 4,000 IU/mL, 10,000 IU/mL, and 40,000/mL.  EPREX, ERYPO 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.	
<b>Is/will the product be subject to additional monitoring in the EU?</b>	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

## PART II: SAFETY SPECIFICATION

### Module SI: 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 1.73 m<sup>2</sup>) 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:**

Anemia develops early in the course of renal disease and progresses with loss of renal function (Astor 2002; Kazmi 2001). Approximately 5% of patients with an eGFR between 30 and 59 mL/min/1.73 m<sup>2</sup> body surface area (BSA) and 44% of patients with eGFR between 15 and 29 mL/min/1.73 m<sup>2</sup> BSA are anemic (Astor 2002). In patients who have progressed to ESRD,

anemia is a ubiquitous comorbidity (United States Renal Data System [USRDS] 2010). In the United States, anemia (defined as serum HGB levels  $\leq 12$  g/dL in women and  $\leq 13$  g/dL in men), was twice as prevalent in people with CKD (15.4%) as in the general population (7.6%). The prevalence of anemia 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 anemia reported being treated for anemia 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 pediatric 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 (ERA) and European Dialysis and Transplantation Association (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 pediatric RRT was 5.5 per million of the age-related population (pmarp). In 9 countries that collected data from pediatric and adult centers 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 National Institute 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 pediatric and adult centers, the prevalence rate was 58.0 pmarp for children aged 0 to 19 years and 109.0 for children aged 15 to 19 years (Chesnaye 2014). In 2012 in the United States, 7,522 children (<19 years old) had prevalent ESRD, which represents a 1.3% decrease from the previous year (Saran 2015).

In the United States, anemia 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 anemia (McClellan 2002; McClellan 2004). Among children, as among adults, the prevalence of anemia 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 anemia increased from 18.5% in Stage 2 CRF to 68% in Stage 5 CRF (Staples 2009).

Among pediatric patients with CRF, anemia, (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 pediatric CRF usually progresses to ESRD by age 20 (up to 68% of patients overall) (Ardissino 2003). Therefore, it is likely that nearly all pediatric patients, other than those with mild CRF, will at some point develop anemia, either as they progress toward ESRD, or at an earlier stage of the disease.

### ***Demographics of the Population in the Authorized Indication - Age, Sex, 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 Kingdom in 2010, 92.9% of patients with Stage 3 to 5 CKD were over 60 years of age, and only 0.5% were between the ages of 18 and 39 (Jameson 2014).

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

#### ***Sex***

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

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

### ***Race***

In the most recent USRDS using NHANES data from 2007 to 2012, the prevalence of all CKD was 13.9% for non-Hispanic Whites, 15.9% for non-Hispanic Blacks, and 11.7% for Other (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 Anemia in Early Renal Insufficiency study (McClellan 2004), 2 thresholds for anemia were defined; the first at a HGB concentration of  $\leq 12$  g/dL and the other at a HGB concentration of  $\leq 10$  g/dL. The study demonstrated that, relative to Caucasian patients, the odds ratios (ORs) for having anemia 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 hyperuricemia (Tsai 2016). Other risk factors include autoimmune diseases, systemic infections, urinary tract infections, nephrolithiasis, lower urinary tract obstruction, hyperuricemia, acute kidney injury, and a family history of the disease. Sociodemographic factors that increase the risk of CKD include older age, black race, smoking, heavy alcohol use, and

obesity (Drawz 2015). According to data from the United Kingdom (UK) Renal Registry, the prevalence of RRT was also higher in socially deprived areas of the United Kingdom.

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

### **Main 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 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 anemia, 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 (CVD) (Stringer 2013). Symptoms of advanced CKD include chest pain, dry skin, feeling tired, headaches, loss of appetite, muscle cramps, nausea/vomiting and weight loss. Anemia commonly occurs in people with CKD. Anemia might begin to develop in the early stages of CKD, when someone has 20 to 50% of normal kidney function, and the anemia tends to worsen as CKD progresses. (NIDDK, 2014a)

In a large retrospective study among patients with incident CRF in a health maintenance organization in the United States, patients with the most severe anemia (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 anemic (Thorp 2009). Anemia 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, CVD accounts for more than half of all deaths, and after a hospitalization 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 hospitalization for those with CRF compared with those without CRF was 1.4 (95% CI: 1.2, 1.8) and RR for anemia (relative to those without anemia) was 1.6 (95% CI: 1.2, 2.2). Relative risk for both CRF and anemia 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 anemia 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 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 pediatric 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, ERA, and 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:**

#### Adults

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

## Children

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

## Cancer

### **Incidence:**

A review summarized that anemia 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 anemia prevalence was dependent on the definition of anemia; for example, 7% of patients with Hodgkin's disease had anemia when the condition was defined as a HGB level <90.0 g/L while as many as 86% of patients had anemia when it was defined as a HGB value <110 g/L. Prevalence also varied by cancer type and disease state; 40% of patients with early-stage colon tumors and nearly 80% of patients with advanced disease had anemia (Knight 2004).

### **Prevalence:**

The European Cancer Anemia Survey (ECAS) (Ludwig 2004) was conducted to document the prevalence, incidence, evolution, severity, and management of anemia in a large, representative population of European patients with cancer. It was a prospective, epidemiologic, observational survey conducted in 748 centers in 24 European countries. It defined anemia 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 anemia increased with the number of cycles of chemotherapy and varied according to cancer type and therapy. Reports from the ECAS estimate the incidence of anemia to be 59.8% for patients with breast cancer and 74.8% for patients with gynecologic cancer, while 62.4% of patients with breast cancer and 81.4% of patients with gynecologic cancer were anemic at some time during the survey. Similarly, 83.3% of patients with lung cancer who received chemotherapy were anemic at some time during the survey (Barrett Lee 2005; Kosmidis 2005). Another analysis of ECAS data reported that for lymphoma and multiple myeloma patients anemia prevalence was 72.9%, and incidence in chemotherapy patients was 55.4% (Birgegård 2006). In patients not receiving antineoplastic treatment, anemia 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 tumors, 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 tumor 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 anemia affects a large proportion of cancer patients regardless of the type of tumor.

***Demographics of the Population in the Authorized Indication – Age, Sex, Racial and/or Ethnic Origin and Risk Factors for the Disease******Age***

Anemia 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 anemia was 63 years (Steggmann 2013). Based on data from the ECAS, 44% of elderly patients (>69 years) were anemic 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 anemia (HGB levels below 12 g/dL), reported anemia prevalence of 45.6% for those ≤65 years, and 52.8% for those >65 (Link 2013).

***Sex***

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

**Main Existing Treatment Options:**

Treatment options for treating anemia 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:**

Anemia 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. Anemia can lead to fatigue and decreased quality of life in these patients, so management of this condition is important (Aapro 2012). Also, anemia in cancer patients has been linked to poorer outcomes and treatment response (Blohmer 2005).

Anemia may adversely affect survival in patients with cancer. In a comprehensive literature review of survival with and without anemia, an association of anemia with reduced survival times was observed consistently for carcinoma of the lung, cervix, head and neck, prostate, lymphoma, and multiple myeloma (Caro 2001). Similarly, survival probability for cancer patients with anemia severity ≥Grade 2 (HGB <10.0 g/dL) was significantly lower than for patients with no anemia (Nakamura 2011). A recent systematic review of studies on outcomes of blood transfusions for anemia 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, CVD 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 practiced anywhere on a very large scale but it is moderately common (4.6% to 7.8% of allogeneic 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 orthopedic 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 orthopedic 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 anemic 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 Authorized Indication – Age, Sex, 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 orthopedic 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 anemic, hypovolemic, or having a low blood count before surgery.

**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 hospitalization, 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 anemia prevalence in patients undergoing major orthopedic surgery reported preoperative anemia 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 anemia 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 anemic 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 anemia (Jans 2014) and an Austrian study reported preoperative anemia rates of 17% and 16% for THR and TKR respectively (Gombotz 2014).

***Demographics of the Population in the Authorized Indication – Age, Sex, 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 utilization rates were observed in men and women in 3 studies based in the United States, Denmark, and England (Singh 2011).

***Risk Factors for the Disease***

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

**Main 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 examining THR and TKR procedures reported that 12.8% of the patients had postoperative anemia. The mortality rate of 1.1% for those with preoperative anemia was significantly higher than the mortality rate for those who did not have anemia (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 anemia in patients undergoing major orthopedic surgery observed both preoperative and postoperative anemia 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 anemic versus non-anemic patients (Spahn 2010).

### **Important Co-morbidities:**

Important co-morbidities in surgery patients include obesity, osteoarthritis, CVD, and hypertension.

### **Adult Patients with Low- or Intermediate-1-risk MDS**

#### **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 standardized 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 Organization classification was 1.14 per 10,000 persons (age-standardized 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 standardized prevalence: 0.81 per 10,000 persons) (Neukirchen 2011).

## ***Demographics of the Population in the Authorized Indication – Age, Sex, 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 UK data demonstrated that the median age at diagnosis is 75.7 years (HMRN 2015).

### Race

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

### Geography

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

### Risk Factors for the Disease

A review noted that the etiology 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 anemia, and neurofibromatosis, as well as MDS occurring in young adults or in families with other cases of MDS, acute myeloid leukemia (AML), or aplastic anemia. Environmental factors could include previous use of chemotherapy, especially alkylating agents and purine analogues radiotherapy or ionizing radiation, and tobacco smoking. Recognized occupational factors include benzene and its derivatives, while excess MDS cases have also been observed in agricultural and industrial workers.

### **Main 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, such as primary allogeneic stem cell transplantation. A high proportion of MDS patients are not eligible for potentially curative treatment due to advanced 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 anemia. 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 anemia. 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 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 CVD, diabetes, cerebrovascular diseases, and medical treatments for prior malignancies.

## PART II: SAFETY SPECIFICATION

### Module SII: Nonclinical Part of the Safety Specification

Key Safety Findings	Relevance to Human Usage
<b><u>Toxicity</u></b>	
<b>Single &amp; repeat-dose toxicity</b>	
<p>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 feces, and slight elevations of lactate dehydrogenase in dogs at 20,000 units/kg, as well as changes in hematology 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.</p>	<p>In repeated-dose toxicological 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 hemodialysis patients 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).</p>
<p>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 feces, and slight elevations of lactate dehydrogenase in dogs at 20,000 units/kg, as well as changes in hematology 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.</p>	<p>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 hemorrhage, and transient ischemic attacks) have been reported.</p>
<p>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 polycythemia that developed as a result of prolonged overstimulation of RBC production.</p>	
<p>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 <math>\geq 100</math> units/kg/day. As a result of high systemic epoetin alfa concentrations, extramedullary hematopoiesis was seen in spleen and liver, and depletion of iron stores and myelofibrosis was seen in the bone marrow in rats and dogs. The</p>	

<b>Key Safety Findings</b>	<b>Relevance to Human Usage</b>
<p>increased severity with time and/or dose suggests a potential for bone marrow toxicity resulting from sustained or marked stimulation of erythropoiesis.</p>	
<p>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.</p>	
<p>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.</p>	
<p>Toxicology studies were not conducted in renally impaired animals.</p>	
<b>Reproductive toxicity</b>	
<p>The administration of epoetin alfa does not impair fertility in rats.</p>	<p>There is no relevance to humans.</p>
<b>Developmental toxicity</b>	
<p>The administration of epoetin alfa does not result in embryo-fetal toxicity in rats or rabbits. A peri- and postnatal developmental toxicology study in rats showed no effect on maturation of offspring.</p>	
<p>In animal studies, epoetin alfa has been shown to decrease fetal body weight, delay ossification, and increase fetal mortality when given in weekly doses of approximately 20 times the recommended human weekly dose.</p>	<p>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 polycythemia seen in the dams.</p>
<p>Findings from repeated-dose toxicology studies in juvenile dogs and monkeys were consistent with those seen in adult animals.</p>	
<b>Genotoxicity</b>	
<p>Epoetin alfa does not induce bacterial gene mutation (Ames test), chromosomal aberrations in mammalian cells, gene mutation at the hypoxanthine-guanine phosphoribosyltransferase locus, nor micronuclei in mice administered IV doses up to 500,000 units/kg.</p>	<p>These studies demonstrate that epoetin alfa has low potential to inflict genetic damage when administered to humans.</p>

<b>Key Safety Findings</b>	<b>Relevance to Human Usage</b>
<p data-bbox="203 212 402 243"><b>Carcinogenicity</b></p> <p data-bbox="203 260 776 394">As EPREX is a biotechnology-derived pharmaceutical product, rodent carcinogenicity studies were not conducted, consistent with ICH S6(R1) guidance.</p> <p data-bbox="203 411 776 709">Long-term carcinogenicity studies have not been conducted. Conflicting reports in the literature, based on in vitro findings from human tumor samples, suggest erythropoietins may play a role as tumor proliferators. This is of uncertain significance in the clinical situation. Nonclinical studies have shown that treatment with ESAs does not enhance tumor progression directly or through enhanced angiogenesis/vasculogenesis.</p>	<p data-bbox="805 260 1425 527">The risk of tumor initiation or proliferation of established tumors 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 anemic patients with metastatic breast cancer receiving EPREX and chemotherapy. Refer to SVII.3 for additional details regarding Trial EPOANE-3010.</p>
<p data-bbox="203 726 467 758"><b><u>Safety pharmacology</u></b></p> <p data-bbox="203 774 776 842"><b>Cardiovascular system (including potential for QT interval prolongation)</b></p> <p data-bbox="203 858 776 1224">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.</p> <p data-bbox="203 1241 402 1272"><b>Nervous system</b></p> <p data-bbox="203 1289 776 1923">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 behavior, 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.</p>	<p data-bbox="805 858 1425 1056">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.</p> <p data-bbox="805 1289 1425 1388">There are no risks identified in nonclinical studies that haven't been adequately addressed in clinical trials.</p>

<b>Key Safety Findings</b>	<b>Relevance to Human Usage</b>
<b>Other</b>	
Immunogenicity	
Antibodies to erythropoietin can be generated in preclinical species. In repeated-dose toxicology studies, Ab titers were of low frequency, but the Ab response can be stimulated by the use of adjuvants and an aggressive immunization 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 postauthorization usage and is considered an important identified risk and is described in detail in Module SVII.3 of this RMP.
Hepatotoxicity	
Systemic toxicity studies did not show hepatotoxicity and therefore no further hepatotoxicity studies were conducted.	There are no nonclinical data to indicate that there would be any hepatotoxicity in humans.
Mechanisms for drug interactions	
None	Not applicable
<b>Other toxicity-related information or data</b>	
None	Not applicable

Ab=antibody; CRF=chronic renal failure; DVT=deep vein thrombosis; ESA=erythropoiesis-stimulating agent; HCT=hematocrit; HGB=hemoglobin; 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 polycythemia (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

## **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 enrolled 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 program before elective surgery.

##### Surgery Indication

The efficacy and safety of epoetin alfa in patients undergoing orthopedic surgery was demonstrated in 11 clinical trials. A total of 2,940 patients undergoing orthopedic 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 orthopedic surgery, Trial H87-083, which enrolled 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 randomized, 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 anemic patients with MDS. Trial EPOANE3018 was conducted to demonstrate that epoetin alfa treatment reduces the

proportion of anemic 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 randomized, 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 summarized in this document is limited to the clinical trials for which patient-level data are available. As the start of the clinical trial program for EPREX dates back to the mid-1980s, available data are presented below. The following sections describe the overall clinical trial program with a data cutoff date of 14 March 2017 with the tables below summarizing available patient-level data. This database includes 93 trials that enrolled over 21,000 patients, of whom >70% (15,349 patients) were exposed to epoetin alfa.

#### **Exposure in Randomized Clinical Trials**

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

- Trials in CRF – Dialysis: EP86-001 (CEO-C01), EP86-004 (2)
- Trials in CRF – 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 randomized clinical trials population is summarized in Tables SIII.1 through SIII.4 for all subjects by duration, by age group and sex, 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 Randomized Clinical Trials Population**

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

Duration of Exposure	INDICATION: All	
	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

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Exposure by Duration; All Randomised Controlled Clinical Trials

Duration of Exposure	INDICATION: Chronic Renal Failure – Dialysis	
	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

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## 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.

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## 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

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## 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

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## 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).

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## 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

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**Table SIII.2: Age Group and Sex: The Randomized Clinical Trials Population**

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

Age Group	INDICATION: All			
	Men Patients (N=2361)	Person-months	Women Patients (N=5234)	Person-months
<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

Age Group	INDICATION: Chronic Renal Failure – Dialysis			
	Men		Women	
	Patients (N=57)	Person-months	Patients (N=40)	Person-months
<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

Age Group	INDICATION: Chronic Renal Failure – Pre-dialysis			
	Men		Women	
	Patients (N=226)	Person-months	Patients (N=238)	Person-months
<18 years	0	0.00	1	4.57
18 - 39 years	23	251.6	29	277.7
40 - 49 years	31	276.2	29	387.1
50 - 59 years	42	310.7	29	150.6
60 - 64 years	28	173.7	23	304.7
65 - 69 years	35	176.5	25	153.9
70 - 74 years	31	243.4	15	105.0
75 - 79 years	17	109.7	18	89.89
80 - 84 years	6	27.60	21	96.36
>=85 years	13	55.82	48	191.1
Missing	0	0.00	0	0.00
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-7472179Z\_RMP\DBR\_RMP\_2018\RE\_RMP\_2018\_EU\tsub05b.sas] 16JAN2018, 21:57

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

Age Group	INDICATION: Oncology			
	Men		Women	
	Patients (N=1504)	Person-months	Patients (N=3819)	Person-months
<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-7472179Z\_RMP\DBR\_RMP\_2018\RE\_RMP\_2018\_EU\tsub05c.sas] 16JAN2018, 21:57

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

Age Group	INDICATION: Autologous Blood Donation			
	Men		Women	
	Patients	Person-months	Patients	Person-months
	(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-7472179Z\_RMP\DBR\_RMP\_2018\RE\_RMP\_2018\_EU\tsub05d.sas] 16JAN2018, 21:57

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

Age Group	INDICATION: Surgery			
	Men		Women	
	Patients	Person-months	Patients	Person-months
	(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-7472179Z\_RMP\DBR\_RMP\_2018\RE\_RMP\_2018\_EU\tsub05e.sas] 16JAN2018, 21:57

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

Age Group	INDICATION: MDS			
	Men		Women	
	Patients	Person-months	Patients	Person-months
	(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\DR\_RMP\_2018\RE\_RMP\_2018\_EU\tsub05g.sas] 16JAN2018, 21:57

## Table III.3: Exposure by Dose: The Randomized Clinical Trials Population

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

Initial dose level	INDICATION: All	
	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\DR\_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 Randomized 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 <sup>a</sup>		(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 <sup>b</sup>	2385	

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

<sup>a</sup> 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

<sup>b</sup> 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-7472179Z\_RMPDBR\_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

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## Exposure by Special Population; All Randomised Controlled Clinical Trials

INDICATION: Chronic Renal Failure – Pre-dialysis			
Population	Category at Baseline	Patients (N=464) (n=395)	Person-months
Total			
Hepatic Impairment			
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.

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## Exposure by Special Population; All Randomised Controlled Clinical Trials

INDICATION: Oncology			
Population	Category at Baseline	Patients	Person-months
Total		(N=5323)	
Hepatic Impairment <sup>a</sup>		(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 <sup>b</sup>	1648	

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

<sup>a</sup> 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.

<sup>b</sup> 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

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## 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 <sup>a</sup>		(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 <sup>b</sup>	204	

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

<sup>a</sup> 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.

<sup>b</sup> 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

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## Exposure by Special Population; All Randomised Controlled Clinical Trials

INDICATION: Surgery			
Population	Category at Baseline	Patients	Person-months
Total		(N=1207)	
Hepatic Impairment <sup>a</sup>		(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 <sup>b</sup>	533	

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

<sup>a</sup> 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.

<sup>b</sup> 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)

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## 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

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## 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: Correction of Haemoglobin and Outcomes in Renal Insufficiency (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 summarized in Tables SIII.5 through SIII.8 for all subjects by duration, by age group and sex, 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

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## 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)

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## 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

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## 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

Duration of Exposure	INDICATION: MDS	
	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 III.6: Age and Sex: All Clinical Trials Populations

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

Age Group	INDICATION: All			
	Men		Women	
	Patients	Person-months	Patients	Person-months
	(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

Age Group	INDICATION: Chronic Renal Failure – Dialysis			
	Men		Women	
	Patients	Person-months	Patients	Person-months
	(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-7472179Z\_RMP\DR\_RMP\_2018\RE\_RMP\_2018\_EU\sub015a.sas] 16JAN2018, 21:58

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

Age Group	INDICATION: Chronic Renal Failure – Pre-dialysis			
	Men		Women	
	Patients	Person-months	Patients	Person-months
	(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-7472179Z\_RMP\DR\_RMP\_2018\RE\_RMP\_2018\_EU\sub015b.sas] 16JAN2018, 21:58

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

Age Group	INDICATION: Oncology			
	Men		Women	
	Patients	Person-months	Patients	Person-months
	(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-7472179Z\_RMP\DR\_RMP\_2018\RE\_RMP\_2018\_EU\tsub015c.sas] 16JAN2018, 21:58

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

Age Group	INDICATION: Autologous Blood Donation			
	Men		Women	
	Patients	Person-months	Patients	Person-months
	(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-7472179Z\_RMP\DR\_RMP\_2018\RE\_RMP\_2018\_EU\tsub015d.sas] 16JAN2018, 21:59

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

Age Group	INDICATION: MDS			
	Men		Women	
	Patients (N=69)	Person-months	Patients (N=43)	Person-months
<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

Age Group	INDICATION: Surgery			
	Men		Women	
	Patients (N=378)	Person-months	Patients (N=974)	Person-months
<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

Initial dose level	INDICATION: All	
	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-7472179V\_RMP\DR\_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-7472179Z\_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-7472179Z\_RMP\DBR\_RMP\_2018\RE\_RMP\_2018\_EU\tsub013b.sas] 16JAN2018, 21:58

## Exposure by Dose; All Clinical Trials Including Open Extension

Initial dose level	INDICATION: Oncology	
	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

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## Exposure by Dose; All Clinical Trials Including Open Extension

Initial dose level	INDICATION: Autologous Blood Donation	
	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

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## Exposure by Dose; All Clinical Trials Including Open Extension

Initial dose level	INDICATION: Surgery	
	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)

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## 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.

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**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 <sup>a</sup>		(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 <sup>b</sup>	2629	

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

<sup>a</sup> 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.

<sup>b</sup> 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

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## 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)

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## 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

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## Exposure by Special Population; All Clinical Trials Including Open Extension

INDICATION: Oncology			
Population	Category at Baseline	Patients	Person-months
Total		(N=5827)	
Hepatic Impairment <sup>a</sup>		(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 <sup>b</sup>	1808	

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

<sup>a</sup> 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.

<sup>b</sup> 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

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## 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 <sup>a</sup>		(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 <sup>b</sup>	204	

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

<sup>a</sup> 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.

<sup>b</sup> 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

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## Exposure by Special Population; All Clinical Trials Including Open Extension

INDICATION: Surgery			
Population	Category at Baseline	Patients	Person-months
Total		(N=1352)	
Hepatic Impairment <sup>a</sup>		(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 <sup>b</sup>	580	

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

<sup>a</sup> 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.

<sup>b</sup> 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)

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## 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 <sup>b</sup>	37	

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

<sup>a</sup> 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.

<sup>b</sup> 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.

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## PART II: SAFETY SPECIFICATION

### Module SIV: Populations Not Studied in Clinical Trials

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

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##### Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

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##### Pure red cell aplasia

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Reason for being an exclusion criterion Pure red cell aplasia is a very rare and serious condition and was discovered through postauthorization surveillance. Patients who develop pure red cell aplasia (PRCA) following treatment with any erythropoietin should not receive EPREX or any other erythropoietin and will have alternative treatment options for anemia.

Considered to be included as missing information No

Rationale (if not included as missing information) Considered to be an important identified risk

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##### Uncontrolled Hypertension

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Reason for being an exclusion criterion Hypertension is the most frequent adverse drug reaction (ADR) 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 clinical trials were conducted. Hypertension/Hypertensive crisis has been removed as an important identified risk when aligning the RMP with GVP Module V, rev 2.

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##### Hypersensitivity

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

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.

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### Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

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#### Severe cardiac or cerebral disease

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Reason for being an exclusion criterion Patients with severe cardiac or cerebral disease are at greater risk for Thrombotic vascular events and CHF.

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.

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#### Seizures

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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 clinical trials were conducted. Hypertension/Hypertensive crisis has been removed as an important identified risk when aligning the RMP with GVP Module V, rev 2.

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#### Pregnancy

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Reason for being an exclusion criterion It is common practice not to include pregnant women in clinical trials.

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 adequate and well-controlled studies 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 fetus. The use of epoetin alfa is not recommended in pregnant surgical patients participating in an autologous blood predonation program.

This product has been marketed for over 25 years and postmarketing data have not shown any change in benefit/risk profile with regards to pregnancy.

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

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions or adverse reactions with a long latency. Rare ADRs ( $\geq 1/10,000$  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 Program(s)

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

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
<b>Patients with relevant comorbidities:</b>	
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 $> 2.5$ ULN at baseline, 268 patients with bilirubin levels $> 1.5$ ULN at baseline, and 289 patients with alkaline phosphatase levels $> 2.5$ ULN at baseline were exposed to EPREX in clinical trials.
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 program 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 Hemoglobin and Outcomes in Renal Insufficiency (CHOIR, PR00-06-014) trial, for example, evaluated 1,432 anemic patients with CRF. Some of the patients in this trial had comorbidities such as MI, stroke, and CHF hospitalizations.
Immunocompromised patients	Renal transplant patients receiving immunosuppressive therapy have been treated with EPREX in clinical trials.  Cancer and MDS patients in clinical trials, either as a function of the disease, or of their chemotherapy, are immunocompromised.

Type of Special Population	Exposure
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
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 program

### Summary of Missing Information Due to Limitations of the Clinical Trial Program

Important identified risks	None
Important potential risks	None
Missing information	None

## **PART II: SAFETY SPECIFICATION**

### **Module SV: Postauthorization Experience**

#### **SV.1. Postauthorization Exposure**

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

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

- Chronic renal failure requiring dialysis
- Chronic renal failure not yet requiring dialysis (predialysis)
- Cancer
- Surgery
- Human immunodeficiency virus (HIV) infection <sup>1</sup>

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 postmarketing exposure from first product launch in 1989 through 31 August 2021 was ██████ PY (data on postmarketing exposure in the ABD indication are not available). The following tables show worldwide EPREX postauthorization exposures by year and indication and EPREX postauthorization exposures by year and route of administration in patients with CRF (data available through August 2021). 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.

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<sup>1</sup> 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****Worldwide Epoetin Alfa Postmarketing Exposures by Time Period and Indication in Person Years (Cumulative to 31 August 2021)**

Indication	1989-2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Cumulative Total <sup>e</sup>
Dialysis <sup>a</sup>	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	108,943	129,819	105,273	96,053	65,622	4,312,449
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	23,679	28,381	25,211	24,204	15,988	650,700
Cancer <sup>b</sup>	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	15,279	16,680	13,524	12,126	7,653	501,799
Surgery <sup>c</sup>	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	1,353	1,666	1,427	1,276	796	48,443
HIV	1,420	4	6	80	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1,511
<b>Total<sup>d</sup></b>	<b>1,991,942</b>	<b>202,038</b>	<b>201,590</b>	<b>199,640</b>	<b>219,260</b>	<b>225,755</b>	<b>228,573</b>	<b>224,715</b>	<b>213,243</b>	<b>206,225</b>	<b>203,484</b>	<b>189,177</b>	<b>184,724</b>	<b>166,727</b>	<b>162,855</b>	<b>149,254</b>	<b>176,547</b>	<b>145,435</b>	<b>133,658</b>	<b>90,059</b>	<b>5,514,901</b>

Key: HIV=Human immunodeficiency virus; ICU=Intensive Care Unit.

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 CRF)****Worldwide Postmarketing Exposure by Year and Route of Epoetin Alfa Administration Among Patients with CRF**

	1989-2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Cumulative Total
<b>Renal Dialysis</b>																					
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	76,308	90,793	76,676	70,902	46,649	1,971,468
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	32,635	39,027	28,597	25,150	18,973	820,450
% IV Exposure	30%	82%	87%	83%	72%	73%	71%	71%	71%	72%	71%	71%	70%	69%	69%	70%	70%	73%	74%	71%	71%
% SC Exposure	70%	18%	13%	17%	28%	27%	29%	29%	29%	28%	29%	29%	30%	31%	31%	30%	30%	27%	26%	29%	29%
<b>Pre-Dialysis Renal Disease</b>																					
IV Exposure (person years)	114	782	855	551	1,037	943	637	527	448	415	383	298	289	257	294	330	702	681	529	251	10,324
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	23,349	27,679	24,530	23,675	15,737	504,047
% IV Exposure	0%	8%	10%	6%	3%	3%	2%	2%	1%	1%	1%	1%	1%	1%	1%	1%	2%	3%	2%	2%	2%
% SC Exposure	100%	92%	90%	94%	97%	97%	98%	98%	99%	99%	99%	99%	99%	99%	99%	99%	98%	97%	98%	98%	98%

Key: CRF=chronic renal failure; IV=intravenous; SC=subcutaneous.

Note: Data through 31 August 2021.

### Additional Stratifications for Epoetin Alfa

Patient exposure was estimated by calculation from Intercontinental Medical Statistics (IMS) Multinational Integrated Data Analysis System (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 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 Sex Presented as a Percentage of Prescription Sales*

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

Further splits such as sex 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.

**Table SV.3 Postmarketing (Nonstudy) Epoetin Alfa Exposure by Age Group in the EU (01 April 2015 to 31 March 2021)**

Age Groups (Years)	EU <sup>a</sup> (1,075,649 Rx <sup>b</sup> )
0 to 17	0.10%
18 to 35	1.10%
36 to 64	14.70%
65+	84.11%

**Key:** EU=European Union; Rx=Prescriptions.

a: Data stratified by age are only available in France, Germany, Italy, Spain, and United Kingdom.

b: Includes retail channels.

**Table SV.4 Postmarketing (Nonstudy) Epoetin Alfa Exposure by Age Group Outside the EU (01 April 2015 to 31 March 2021)**

Age Groups (Years)	Non-EU <sup>a</sup> (2,611,041 Rx <sup>b</sup> )
0 to 17	0.13%
18 to 35	1.29%
36 to 64	22.33%
65+	76.15%
Age unspecified	0.10%

**Key:** EU=European Union; Rx=Prescriptions.

a: Data stratified by age are only available in Canada and the United States.

b: Includes retail channels.

**Table SV.5 Postmarketing (Nonstudy) Epoetin Alfa Exposure by Sex (01 April 2015 to 31 March 2021)**

<b>Country</b>	<b>Females<sup>a</sup></b>	<b>Males<sup>a</sup></b>	<b>Patient Sex Unidentified<sup>a</sup></b>
Canada (59,520 Rx <sup>b</sup> )	50.03%	49.97%	0.00%
France (11,727 Rx <sup>b</sup> )	29.68%	70.32%	0.00%
Germany (28,766 Rx <sup>b</sup> )	42.57%	57.43%	0.00%
Italy (791,832 Rx <sup>b</sup> )	56.43%	43.57%	0.00%
Spain (237,990 Rx <sup>b</sup> )	48.57%	51.43%	0.00%
United Kingdom (5,334 Rx <sup>b</sup> )	58.59%	41.41%	0.00%
United States (2,551,521 Rx <sup>b</sup> )	51.36%	48.18%	0.46%

**Key:** Rx=Prescriptions

a: Data are only available for Canada, France, Germany, Italy, Spain, United Kingdom, and the United States.

b: Includes retail channels.

## **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 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 IV or SC. It is not subject to abuse when administered through regulated channels.

## **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 initial RMP

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

Not applicable.

#### **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 postmarketing experience for some risks.

##### **Important identified risks:**

1. Pure red cell aplasia

##### **Important potential risks:**

1. Disease progression
2. Survival impact

##### **Missing Information:**

None

MedDRA version 19.1 was used to classify the clinical trials adverse event information that is summarized 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 antibodies (Abs) to erythropoietin causes an isolated disorder of erythropoiesis that leads to a severe, isolated anemia 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).

Anemia 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 postmarketing setting and is also described in the current prescribing information for EPREX.

**Characterization of the Risk:****Frequency (95% Confidence Interval), Seriousness, Outcomes, and Severity of Pure Red Cell Aplasia in Clinical Trials**

	INDICATION: Chronic Renal Failure – Dialysis		
	Epoetin alfa (N=2046)	Non-ESA control (N=46)	Odds Ratio <sup>a</sup> (95% CI)
Randomised Controlled Trials <sup>b</sup>	97	46	
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%)	
Trials without control <sup>c</sup>	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%)	

<sup>a</sup> The stratified Mantel-Haenszel odds ratio (stratified by study) was used.

<sup>b</sup> Includes EP86-001 (CEO-C01), EP86-004

<sup>c</sup> 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 (95% Confidence Interval), Seriousness, Outcomes, and Severity of Pure Red Cell Aplasia in Clinical Trials

	INDICATION: Chronic Renal Failure – Pre-dialysis		Odds Ratio <sup>a</sup> (95% CI)
	Epoetin alfa (N=5610)	Non-ESA control (N=325)	
Randomised Controlled Trials <sup>b</sup>	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 <sup>c</sup>	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%)	

<sup>a</sup> The stratified Mantel-Haenszel odds ratio (stratified by study) was used.

<sup>b</sup> Includes EPO-AUS-14, EPO-CAN-10, EPO-ITA-7, EPOCKD2002, G86-011, H87-054

<sup>c</sup> 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.

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**Frequency (95% Confidence Interval), Seriousness, Outcomes, and Severity of Pure Red Cell Aplasia in Clinical Trials**

	INDICATION: Oncology		Odds Ratio <sup>a</sup> (95% CI)
	Epoetin alfa (N=5827)	Non-ESA control (N=4719)	
Randomised Controlled Trials <sup>b</sup>	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 <sup>c</sup>	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%)	

<sup>a</sup> The stratified Mantel-Haenszel odds ratio (stratified by study) was used.

<sup>b</sup> 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-0, 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

<sup>c</sup> 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.

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**Frequency (95% Confidence Interval), Seriousness, Outcomes, and Severity of Pure Red Cell Aplasia in Clinical Trials**


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	INDICATION: Autologous Blood Donation		Odds Ratio <sup>a</sup> (95% CI)
	Epoetin alfa (N=402)	Non-ESA control (N=242)	
Randomised Controlled Trials <sup>b</sup>	402	242	
N			
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)	402	242	
N			
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%)	

<sup>a</sup> The stratified Mantel-Haenszel odds ratio (stratified by study) was used.

<sup>b</sup> 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.

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[TAE03D.rtf] [JNJ-7472179\Z\_RMP\DBR\_RMP\_2018\RE\_RMP\_2018\_EU\tae03d.sas] 16JAN2018, 22:01

### Frequency (95% Confidence Interval), Seriousness, Outcomes, and Severity of Pure Red Cell Aplasia in Clinical Trials

	INDICATION: Surgery		Odds Ratio <sup>a</sup> (95% CI)
	Epoetin alfa (N=1352)	Non-ESA control (N=922)	
Randomised Controlled Trials <sup>b</sup>	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 <sup>c</sup>	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%)	

<sup>a</sup> The stratified Mantel-Haenszel odds ratio (stratified by study) was used.

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

<sup>c</sup> 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-7472179Z\_RMP/DBR\_RMP\_2018/RE\_RMP\_2018\_EU\tae03e.sas] 16JAN2018, 22:01

### Frequency (95% Confidence Interval), Seriousness, Outcomes, and Severity of Pure Red Cell Aplasia in Clinical Trials

	INDICATION: MDS		Odds Ratio <sup>a</sup> (95% CI)
	Epoetin alfa (N=112)	Non-ESA control (N=53)	
Randomised Controlled Trials <sup>b</sup>	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%)	

<sup>a</sup> The stratified Mantel-Haenszel odds ratio (stratified by study) was used.

<sup>b</sup> 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

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

To date, only 2 cases of PRCA have been reported among EPREX-treated patients in clinical trials. Among the [REDACTED] 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 enrolled 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 orthopedic 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 minimize 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 (hemodialysis 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 characterized 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, aluminum intoxication, infection or inflammation, blood loss, and hemolysis and bone marrow fibrosis of any origin) should be investigated.

A paradoxical decrease in HGB and development of severe anemia 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 anemia 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-positive PRCA in CKD/CRF patients for all presentations/formulations and routes of administration since 2004 remain well below the historic peak in 2002.

Anemia 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 tumor growth and proliferation. Although there is no convincing evidence from clinical trials that epoetin alfa promotes tumor growth, theoretical mechanisms include: 1) direct tumor promotion through an interaction with epoetin receptors expressed on the surface of tumor cells, 2) promotion of tumor vascularization leading to promotion of tumor 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.

#### Characterization of the Risk:

### **Frequency (95% Confidence Interval), Seriousness, Outcomes, and Severity of Disease Progression in Clinical Trials**

	INDICATION: Oncology		Odds Ratio <sup>a</sup> (95% CI)
	Epoetin alfa (N=5827)	Non-ESA control (N=4719)	
Randomised Controlled Trials <sup>b</sup>	5323	4719	
N			
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%)	
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%)	

### Frequency (95% Confidence Interval), Seriousness, Outcomes, and Severity of Disease Progression in Clinical Trials

	INDICATION: Oncology		Odds Ratio <sup>a</sup> (95% CI)
	Epoetin alfa (N=5827)	Non-ESA control (N=4719)	
Trials without control <sup>c</sup>	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%)	

<sup>a</sup> The stratified Mantel-Haenszel odds ratio (stratified by study) was used.

<sup>b</sup> 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

<sup>c</sup> 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.

[TAE07C.rtf] [JNJ-7472179Z\_RMP\DR\_RMP\_2018\RE\_RMP\_2018\_EU\tac07c.sas] 09FEB2018, 13:59

**Frequency (95% Confidence Interval), Seriousness, Outcomes, and Severity of Disease Progression in Clinical Trials**

INDICATION: MDS			
	Epoetin alfa (N=112)	Non-ESA control (N=53)	Odds Ratio <sup>a</sup> (95% CI)
Randomised Controlled Trials <sup>b</sup>	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%)	

<sup>a</sup> The stratified Mantel-Haenszel odds ratio (stratified by study) was used.

<sup>b</sup> 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

## Cancer

This important potential risk only involves patients treated for chemotherapy-induced anemia (CIA).

None of the Company's supportive-care trials has rigorously assessed tumor outcomes utilizing methods that would be appropriate to the development of cancer therapeutic agents. In general, trials have lacked the necessary tumor and treatment homogeneity for this assessment because they were designed to evaluate hematologic endpoints, not tumor 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 anemic 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).

Tumor 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 tumor 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 tumor 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 ██████ adult patients treated in all cancer clinical trials, there were ██████ treatment-emergent disease progression event among patients treated with EPREX and ██████ among non-ESA-treated patients. The largest number among patients treated with EPREX were considered Grade 3 (████████) and the largest number among non-ESA-treated patients were also Grade 3 (████████). 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), AML (1 patient in the epoetin alfa group, 2 patients in the placebo group), refractory anemia with excess blasts (1 patient in each group), leukemia (1 patient in the epoetin alfa group), thrombocytopenia (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 anemia (>12 g/dL), or in the setting of cancer-induced anemia 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 tumor 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 CRF trials.

#### Characterization of the Risk:

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

Survival or mortality data were collected in some of the cancer and CRF clinical trials. However, survival in patients with cancer mainly depends on the underlying tumor type and patients in different cancer trials had very different tumor 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 tumor type and patients in different cancer trials had very different tumor 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**

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<b>Important Identified risks</b>	Pure red cell aplasia
<b>Important Potential risks</b>	Disease progression Survival impact
<b>Missing Information</b>	None

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### **PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)**

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

##### **Specific Follow-up Questionnaires for Safety Concerns**

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
None		

#### **III.2. Additional Pharmacovigilance Activities**

None.

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

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

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
<b>Category 1</b> - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
<b>Category 2</b> - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
<b>Category 3</b> - Required additional pharmacovigilance activities				
Not applicable				

## PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

**Table Part IV.1: Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations**

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

**PART V: RISK MINIMIZATION MEASURES**  
**(Including Evaluation of the Effectiveness of Risk Minimization Activities)**

**Risk Minimization Plan**

**V.1. Routine Risk Minimization Measures**

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

Safety Concern	Routine Risk Minimization Activities
Pure red cell aplasia	<p><b>Routine risk communication:</b></p> <ul style="list-style-type: none"> <li>• SmPC Section 4.3</li> <li>• SmPC Section 4.4</li> <li>• PL Section 2</li> <li>• PL Section 4</li> </ul> <p><b>Routine risk minimization activities recommending specific clinical measures to address the risk:</b></p> <ul style="list-style-type: none"> <li>• Monitor HGB levels closely (SmPC Section 4.4)</li> </ul>
Disease progression	<p><b>Routine risk communication:</b></p> <ul style="list-style-type: none"> <li>• SmPC Section 4.4</li> <li>• SmPC Section 5.1</li> <li>• PL Section 2</li> </ul> <p><b>Routine risk minimization activities recommending specific clinical measures to address the risk:</b></p> <ul style="list-style-type: none"> <li>• Monitor HGB levels closely (SmPC Section 4.4)</li> </ul>
Survival impact	<p><b>Routine risk communication:</b></p> <ul style="list-style-type: none"> <li>• SmPC Section 4.4</li> <li>• SmPC Section 5.1</li> <li>• PL Section 2</li> </ul> <p><b>Routine risk minimization activities recommending specific clinical measures to address the risk:</b></p> <p>None</p>

**V.2. Additional Risk Minimization Measures**

Routine risk minimization 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 Minimization Activities**

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

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

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Pure red cell aplasia	<p><b>Routine risk minimization measures:</b></p> <ul style="list-style-type: none"> <li>• SmPC Section 4.3</li> <li>• SmPC Section 4.4, where advice is given to monitor HGB levels closely</li> <li>• PL Section 2</li> <li>• PL Section 4</li> </ul> <p><b>Additional risk minimization measures:</b> None</p>	<p><b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b></p> <ul style="list-style-type: none"> <li>• Targeted Follow-up Questionnaires</li> </ul> <p><b>Additional pharmacovigilance activities:</b> None</p>
Disease progression	<p><b>Routine risk minimization measures:</b></p> <ul style="list-style-type: none"> <li>• SmPC Section 4.4, where advice is given to monitor HGB levels closely</li> <li>• SmPC Section 5.1</li> <li>• PL Section 2</li> </ul> <p><b>Additional risk minimization measures:</b> None</p>	<p><b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b> None</p> <p><b>Additional pharmacovigilance activities:</b> None</p>
Survival impact	<p><b>Routine risk minimization measures:</b></p> <ul style="list-style-type: none"> <li>• SmPC Section 4.4</li> <li>• SmPC Section 5.1</li> <li>• PL Section 2</li> </ul> <p><b>Additional risk minimization measures:</b> None</p>	<p><b>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</b> None</p> <p><b>Additional pharmacovigilance activities:</b> None</p>

## **PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN**

### **Summary of Risk Management Plan for EPREX**

This is a summary of the risk management plan (RMP) for EPREX. The RMP details important risks of EPREX, how these risks can be minimized, and how more information will be obtained about EPREX's risks and uncertainties (missing information).

EPREX's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how EPREX should be used.

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 authorized for use in chronic renal failure (CRF), 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 (SC).

#### **II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks**

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized 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 minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report (PSUR) assessment, so that immediate 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 minimize the risk, so that the medicinal product can be safely administered.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of 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);

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

## II.B. Summary of Important Risks

### Important Identified Risk: Pure Red Cell Aplasia

Evidence for linking the risk to the medicine	Pure red cell aplasia was initially identified in the postmarketing setting and is also described in the current prescribing information for EPREX.
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Risk factors and risk groups	<p><i>Chronic Renal Failure</i></p> <p>Pure red cell aplasia has been reported in patients with CRF who were receiving epoetin alfa by SC administration. Risk factors for antibody (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.</p> <p><i>Cancer</i></p> <p>Risk factors for developing PRCA and patients with cancer are not detailed in the literature.</p> <p><i>Surgery</i></p> <p>Risk factors for developing PRCA and patients undergoing orthopedic surgery are not detailed in the literature.</p>
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**Important Identified Risk: Pure Red Cell Aplasia**

Risk minimization measures	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> <li>• SmPC Section 4.3</li> <li>• SmPC Section 4.4, where advice is given to monitor hemoglobin (HGB) levels closely</li> <li>• PL Section 2</li> <li>• PL Section 4</li> </ul> <p>Additional risk minimization measures:</p> <p>None</p>
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**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 minimization measures	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> <li>• SmPC Section 4.4, where advice is given to monitor HGB levels closely</li> <li>• SmPC Section 5.1</li> <li>• PL Section 2</li> </ul> <p>Additional risk minimization measures:</p> <p>None</p>

**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 CRF 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 tumor type and patients in different cancer trials had very different tumor types.
Risk minimization measures	Routine risk minimization measures: <ul style="list-style-type: none"> <li>• SmPC Section 4.4</li> <li>• SmPC Section 5.1</li> <li>• PL Section 2</li> </ul> Additional risk minimization measures: None

**II.C. Postauthorization Development Plan****II.C.1. Studies Which are Conditions of the Marketing Authorization**

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

**II.C.2. Other Studies in Postauthorization Development Plan**

There are no studies required for EPREX.

## **PART VII: ANNEXES**

### **Table of Contents**

- Annex 1 EudraVigilance Interface
- Annex 2 Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program
- Annex 3 Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan
  - Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP
  - 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
  - Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority
- Annex 4 Specific Adverse Drug Reaction Follow-up Forms
- Annex 5 Protocols for Proposed and Ongoing Studies in RMP Part IV
- Annex 6 Details of Proposed Additional Risk Minimization Measures (if applicable)
- Annex 7 Other Supporting Data (Including Referenced Material)
- Annex 8 Summary of Changes to the Risk Management Plan Over Time

**Annex 1: Eudravigilance Interface**

Not applicable.

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

### 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 Cross-reference to Report
Trial EPOANE3010 Randomised, Open-Label, Multicentre, Phase 3 Study of Epoetin Alfa Plus Standard Supportive Care Versus Standard Supportive Care in Anemic Patients With Metastatic Breast Cancer Receiving Standard Chemotherapy Category 3	Assess the impact on tumor 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 anemia in patients with metastatic breast cancer receiving first-line or second-line chemotherapy.	Disease progression; TVEs, survival impact	01 June 2017
Trial EPOANE4014 Prospective, Immunogenicity Surveillance Registry to Estimate the Incidence of Erythropoietin Antibody-Mediated Pure Red Cell Aplasia Among Subjects With Chronic Renal Failure and Subcutaneous Exposure to Recombinant Erythropoietin Products Category 2	Estimate IR of 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 25 Jan 2012
Trial EPOANE4008 A randomised, open-label, multicentre study evaluating thrombovascular events in subjects with cancer receiving chemotherapy and administered epoetin alfa once or 3 times a week for the treatment of anaemia Category 2	Further evaluate the safety profile of the QW dosing regimen in patients with cancer, with particular focus on the incidence of TVEs	TVEs	Final study report submitted 31 Mar 2010

**Table 2 Annex II: Completed Studies**

Study	Summary of Objectives	Safety Concerns Addressed	Date of Final Study Report Submission Cross-reference to Report
Trial EPOANE4076 <sup>a</sup> A Prospective, Immunogenicity Surveillance Registry of Erythropoiesis-Stimulating Agents with Subcutaneous Exposure in Thailand Category 3	Estimate the incidence of anti-human erythropoiesis and anti-erythropoietin PRCA in patients using any ESA by the SC route.	PRCA	Final report submitted 05 May 2015

Ab=antibody; ESA=erythropoiesis-stimulating agent; IR=incidence rate; MAH=market authorization holder; PRCA=pure red cell aplasia; PRIMIS=Pharmacoepidemiology Registry EPOANE4014 Prospective Immunogenicity Surveillance; PS-80=polysorbate-80; QW=once weekly; SC=subcutaneous; TVE=thrombotic vascular event

<sup>a</sup>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**

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

COVER

**Janssen Research & Development, LLC**

**Global Medical Safety**

Protocol EPO-IMU-001

PATIENT INITIALS	DATE	GLOBAL AE #:
<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>

**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:**

Male     Female

**Race:**  Unknown

White     Black     Asian     Other: \_\_\_\_\_

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

Renal Anemia .....  Yes\*     No

\*If yes - Fill in one choice below.

Pre-Dialysis Renal Failure     Peritoneal Dialysis     Hemodialysis

None

Other, specify: \_\_\_\_\_

Cancer .....  Yes\*\*     No

\*\*If yes, Specify Type or Reason: \_\_\_\_\_

Unknown .....  Yes     No

Other .....  Yes\*\*\*     No

\*\*\*If yes, Specify: \_\_\_\_\_

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

Pre-Dialysis Renal Failure     Peritoneal Dialysis     Hemodialysis     Normal Renal Function



**Janssen Research & Development, LLC**

**Global Medical Safety**

Protocol EPO-IMU-001

GLOBAL AE #:																				
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**6. Was a reticulocyte performed at the time of LOE?**  
<sub>2</sub> Yes\*    <sub>1</sub> No    <sub>98</sub> 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 % ..... [ ]  %<sub>(902)</sub>     Fraction of 1.0<sub>(911)</sub>    Normal Range [ ]

(1210) Reticulocyte Count (absolute) . [ ]  x10<sup>9</sup>/L<sub>(116)</sub>     x10<sup>3</sup>/cu mm<sub>(801)</sub>     /cu mm<sub>(803)</sub>    Normal Range [ ]

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

<sub>1</sub> Eprex<sup>®</sup>    <sub>2</sub> Epoxitin<sup>®</sup>    <sub>3</sub> Espo<sup>®</sup>    <sub>4</sub> Epopen<sup>®</sup>    <sub>5</sub> Globuren<sup>®</sup>    <sub>6</sub> Erypo<sup>®</sup>  
<sub>7</sub> Procrit<sup>®</sup>    <sub>8</sub> Epogen<sup>®</sup>    <sub>9</sub> Culat<sup>®</sup>    <sub>10</sub> Recormon<sup>®</sup>    <sub>11</sub> NeoRecormon<sup>®</sup>    <sub>12</sub> Recopen<sup>®</sup>  
<sub>13</sub> Epogin<sup>®</sup>    <sub>14</sub> Eratin<sup>®</sup>    <sub>15</sub> Aranesp<sup>®</sup>    <sub>16</sub> Haemax<sup>®</sup>    <sub>98</sub> Unknown  
<sub>99</sub> Other, specify: \_\_\_\_\_

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

DOSE	ROUTE <i>Fill in all that apply.</i>	FREQUENCY <i>(x/week) or (x/month)</i>	START DATE	LOT NUMBER																				
1. _____ <input type="radio"/> <sub>1</sub> Pre-fill Syringe <input type="radio"/> <sub>2</sub> Single-Use Vial <input type="radio"/> <sub>3</sub> Multi-Use Vial <input type="radio"/> <sub>99</sub> Other, specify: _____ <input type="radio"/> <sub>98</sub> Unknown	<input type="radio"/> <sub>1</sub> Intravenous (IV) <input type="radio"/> <sub>2</sub> Subcutaneous <input type="radio"/> <sub>98</sub> Unknown	_____	Start date: <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td></tr></table> <small>d d m o n y y</small> Stop date: <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td></tr></table> <small>d d m o n y y</small> OR <input type="radio"/> <sub>98</sub> Unknown																					
2. _____ <input type="radio"/> <sub>1</sub> Pre-fill Syringe <input type="radio"/> <sub>2</sub> Single-Use Vial <input type="radio"/> <sub>3</sub> Multi-Use Vial <input type="radio"/> <sub>99</sub> Other, specify: _____ <input type="radio"/> <sub>98</sub> Unknown	<input type="radio"/> <sub>1</sub> Intravenous (IV) <input type="radio"/> <sub>2</sub> Subcutaneous <input type="radio"/> <sub>98</sub> Unknown	_____	Start date: <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td></tr></table> <small>d d m o n y y</small> Stop date: <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td></tr></table> <small>d d m o n y y</small> OR <input type="radio"/> <sub>98</sub> Unknown																					

**Janssen Research & Development, LLC**  
**Global Medical Safety**

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<b>Question #7 continued.</b>																																				
DOSE	ROUTE <i>Fill in all that apply.</i>	FREQUENCY <i>(x/week)</i>	START DATE	LOT NUMBER																																
3. _____ <input type="radio"/> <sub>1</sub> Pre-fill Syringe <input type="radio"/> <sub>2</sub> Single-Use Vial <input type="radio"/> <sub>3</sub> Multi-Use Vial <input type="radio"/> <sub>99</sub> Other, specify: _____ <input type="radio"/> <sub>98</sub> Unknown	<input type="radio"/> <sub>1</sub> Intravenous (IV) <input type="radio"/> <sub>2</sub> Subcutaneous <input type="radio"/> <sub>98</sub> Unknown	_____	Start date: <table border="1" style="margin: auto; border-collapse: collapse;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td style="text-align: center;">d</td> <td style="text-align: center;">d</td> <td style="text-align: center;">m</td> <td style="text-align: center;">o</td> <td style="text-align: center;">n</td> <td style="text-align: center;">y</td> <td style="text-align: center;">y</td> <td style="text-align: center;">y</td> </tr> </table> Stop date: <table border="1" style="margin: auto; border-collapse: collapse;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td style="text-align: center;">d</td> <td style="text-align: center;">d</td> <td style="text-align: center;">m</td> <td style="text-align: center;">o</td> <td style="text-align: center;">n</td> <td style="text-align: center;">y</td> <td style="text-align: center;">y</td> <td style="text-align: center;">y</td> </tr> </table> <b>OR</b> <input type="radio"/> <sub>98</sub> Unknown									d	d	m	o	n	y	y	y									d	d	m	o	n	y	y	y	
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d	d	m	o	n	y	y	y																													
d	d	m	o	n	y	y	y																													

**8. Were other epoetins taken before LOE?**  
<sub>2</sub> Yes\*    <sub>1</sub> No    <sub>98</sub> 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. _____ _____	<table border="1" style="margin: auto; border-collapse: collapse;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td style="text-align: center;">d</td> <td style="text-align: center;">d</td> <td style="text-align: center;">m</td> <td style="text-align: center;">o</td> <td style="text-align: center;">n</td> <td style="text-align: center;">y</td> <td style="text-align: center;">y</td> <td style="text-align: center;">y</td> </tr> </table>									d	d	m	o	n	y	y	y	<table border="1" style="margin: auto; border-collapse: collapse;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td style="text-align: center;">d</td> <td style="text-align: center;">d</td> <td style="text-align: center;">m</td> <td style="text-align: center;">o</td> <td style="text-align: center;">n</td> <td style="text-align: center;">y</td> <td style="text-align: center;">y</td> <td style="text-align: center;">y</td> </tr> </table> <b>OR</b> <input type="radio"/> <sub>98</sub> Unknown									d	d	m	o	n	y	y	y
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d	d	m	o	n	y	y	y																											
d	d	m	o	n	y	y	y																											

**9. Do you suspect Pure Red Cell Aplasia (PRCA):**    <sub>2</sub> Yes    <sub>1</sub> No

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**10. Has a bone marrow examination (biopsy and / or aspirate) been performed?**  
<sub>2</sub> Yes\*    <sub>1</sub> 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																								
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d	d	m	o	n	y	y																				
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d	d	m	o	n	y	y																				

**11. Has antibody testing been performed on this patient?**   <sub>2</sub> Yes\*    <sub>1</sub> No    <sub>98</sub> Unknown  
*\*If Yes, provide information below for all antibody tests performed.*

DATE OF TEST	METHOD	RESULT	LAB																								
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<b>MEDICAL AND MEDICATION HISTORY</b>				
<b>12. Within 3 months of LOE did the patient have any of the following conditions?</b>				
<i>Fill Yes, No, or Unknown for each.</i>	YES (2)	NO (1)	UNKNOWN (98)	If yes, fill in value with unit or comment.
Parvovirus B19 infection (IgM)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Recent Hepatitis A (confirmed by IgM antibody response)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Recent or Chronic Hepatitis B	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Recent or Chronic Hepatitis C	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Thymoma confirmed by Chest CT Scan	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Iron Deficiency	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Folate Deficiency	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Vitamin B12 Deficiency	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Aluminum Intoxication	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
Hyperparathyroidism	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	

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

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<b>MEDICATIONS</b>																																										
<p><b>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?</b></p> <p><input type="radio"/><sub>2</sub> Yes*    <input type="radio"/><sub>1</sub> No    <input type="radio"/><sub>98</sub> Unknown</p> <p><i>*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.</i></p>																																										
MEDICATIONS	START DATE	STOP DATE																																								
<input type="radio"/> <sub>1</sub> Allopurinol	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table>											d	d	m	o	n	y	y				<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table> <p><b>OR</b> <input type="radio"/><sub>1</sub> Continuing</p>											d	d	m	o	n	y	y			
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<input type="radio"/> <sub>2</sub> Alpha-Methyldopa Dop (Aldomet)	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table>											d	d	m	o	n	y	y				<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table> <p><b>OR</b> <input type="radio"/><sub>1</sub> Continuing</p>											d	d	m	o	n	y	y			
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<input type="radio"/> <sub>3</sub> Anti-thymocyte preparations	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table>											d	d	m	o	n	y	y				<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table> <p><b>OR</b> <input type="radio"/><sub>1</sub> Continuing</p>											d	d	m	o	n	y	y			
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<input type="radio"/> <sub>4</sub> Azathioprine	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table>											d	d	m	o	n	y	y				<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table> <p><b>OR</b> <input type="radio"/><sub>1</sub> Continuing</p>											d	d	m	o	n	y	y			
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<input type="radio"/> <sub>5</sub> Aztreonam	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table>											d	d	m	o	n	y	y				<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table> <p><b>OR</b> <input type="radio"/><sub>1</sub> Continuing</p>											d	d	m	o	n	y	y			
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<input type="radio"/> <sub>6</sub> Carbamazepine	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table>											d	d	m	o	n	y	y				<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table> <p><b>OR</b> <input type="radio"/><sub>1</sub> Continuing</p>											d	d	m	o	n	y	y			
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<input type="radio"/> <sub>7</sub> Cephalothin	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table>											d	d	m	o	n	y	y				<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table> <p><b>OR</b> <input type="radio"/><sub>1</sub> Continuing</p>											d	d	m	o	n	y	y			
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**Janssen Research & Development, LLC**

**Global Medical Safety**

Protocol EPO-IMU-001

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<b>MEDICATIONS from question #13 continued....</b>																																										
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**Janssen Research & Development, LLC**

**Global Medical Safety**

Protocol EPO-IMU-001

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<b>MEDICATIONS from question #13 continued...</b>																																										
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<input type="radio"/> <sub>37</sub> Mycophenolic Mophetil	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table>											d	d	m	o	n	y	y				<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table> <b>OR</b> <input type="radio"/> <sub>1</sub> Continuing											d	d	m	o	n	y	y			
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<input type="radio"/> <sub>27</sub> Rifampin	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table>											d	d	m	o	n	y	y				<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table> <b>OR</b> <input type="radio"/> <sub>1</sub> Continuing											d	d	m	o	n	y	y			
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<input type="radio"/> <sub>28</sub> Rituximab	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table>											d	d	m	o	n	y	y				<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table> <b>OR</b> <input type="radio"/> <sub>1</sub> Continuing											d	d	m	o	n	y	y			
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<input type="radio"/> <sub>39</sub> Sulfamethoxazole	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table>											d	d	m	o	n	y	y				<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table> <b>OR</b> <input type="radio"/> <sub>1</sub> Continuing											d	d	m	o	n	y	y			
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<input type="radio"/> <sub>29</sub> Sulfasalazine	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table>											d	d	m	o	n	y	y				<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table> <b>OR</b> <input type="radio"/> <sub>1</sub> Continuing											d	d	m	o	n	y	y			
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<input type="radio"/> <sub>30</sub> Sulfobromophthalein sodium (bromsulphthalein)	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table>											d	d	m	o	n	y	y				<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table> <b>OR</b> <input type="radio"/> <sub>1</sub> Continuing											d	d	m	o	n	y	y			
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<input type="radio"/> <sub>40</sub> Trimetoprim	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table>											d	d	m	o	n	y	y				<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table> <b>OR</b> <input type="radio"/> <sub>1</sub> Continuing											d	d	m	o	n	y	y			
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**Janssen Research & Development, LLC**

**Global Medical Safety**

Protocol EPO-IMU-001

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<b>MEDICATIONS from question #13 continued....</b>																																										
<i>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.</i>																																										
MEDICATIONS	START DATE	STOP DATE																																								
<input type="radio"/> <sub>31</sub> Tacrolimus	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table>											d	d	m	o	n	y	y				<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table> <b>OR</b> <input type="radio"/> <sub>1</sub> Continuing											d	d	m	o	n	y	y			
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<input type="radio"/> <sub>32</sub> Thiamphenicol	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table>											d	d	m	o	n	y	y				<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table> <b>OR</b> <input type="radio"/> <sub>1</sub> Continuing											d	d	m	o	n	y	y			
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<input type="radio"/> <sub>33</sub> Valproic acid	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table>											d	d	m	o	n	y	y				<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table> <b>OR</b> <input type="radio"/> <sub>1</sub> Continuing											d	d	m	o	n	y	y			
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<input type="radio"/> <sub>34</sub> Zidovudine	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table>											d	d	m	o	n	y	y				<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td> </tr> <tr> <td>d</td><td>d</td><td>m</td><td>o</td><td>n</td><td>y</td><td>y</td><td></td><td></td><td></td> </tr> </table> <b>OR</b> <input type="radio"/> <sub>1</sub> Continuing											d	d	m	o	n	y	y			
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<b>14. Was immunosuppressive or other therapy used if and when PRCA was suspected and/or antibodies were suspected or confirmed?</b> <input type="radio"/> <sub>2</sub> Yes* <input type="radio"/> <sub>1</sub> No <input type="radio"/> <sub>98</sub> Unknown																																											
<i>*If Yes, please provide information below.</i>																																											
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**Janssen Research & Development, LLC**

**Global Medical Safety**

Protocol EPO-IMU-001

GLOBAL AE #:										
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**15. Do you have any samples of the patient's serum prior to LOE available?**  
<sub>2</sub> Yes    <sub>1</sub> No    <sub>98</sub> 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?**  
<sub>2</sub> Yes    <sub>1</sub> No    <sub>98</sub> Unknown

**16. Was the patient transfusion dependent during period of LOE?**  
<sub>2</sub> Yes    <sub>1</sub> No    <sub>98</sub> Unknown

**17. Is the patient currently transfusion dependent?**    <sub>2</sub> Yes    <sub>1</sub> No    <sub>98</sub> 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.***

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**

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

**2. Epoetin Therapy Since PRCA Diagnosis**

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

**3. Treatment for PRCA Since PRCA Diagnosis**

<b>PRCA Treatment</b>	<input type="checkbox"/> <b>Yes</b> <input type="checkbox"/> <b>No</b>
<b>If immunosuppressive or other treatment was administered for PRCA, please provide the following treatment details:</b>	<b>Therapy (drug name):</b> 1) _____ 2) _____
	<b>Dose/Frequency/Route:</b> 1) _____ 2) _____
	<b>Dates of therapy (Month/Year):</b> 1) From _____ / _____ To _____ / _____ 2) From _____ / _____ To _____ / _____
<b>Response to Therapy:</b>	<input type="checkbox"/> Recovered/Resolved <input type="checkbox"/> Improved <input type="checkbox"/> Worsened <input type="checkbox"/> 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 Minimization 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

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## Annex 7.2 Abbreviations

Ab	antibody
ABD	autologous blood donation
ADR	adverse drug reaction
AML	acute myeloid leukemia
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
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 anemia
CKD	chronic kidney disease
CRF	chronic renal failure
CSR	clinical study report
CVD	cardiovascular disease
ECAS	European Cancer Anaemia Survey
EDTA	European Dialysis and Transplantation Association
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ERA	European Renal Association
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
EU	European Union
GFR	glomerular filtration rate
HCT	hematocrit
HGB	hemoglobin
HIV	human immunodeficiency virus
HMRN	Haematological Malignancy Research Network
HR	hazard ratio
IMS	Intercontinental Medical Statistics
IPSS	International Prognostic Scoring System
IR	incidence rate
ISAC	Independent Safety Advisory Committee
IU	international units
IV	intravenous(ly)
MAH	marketing authorization holder
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MIDAS	Multinational Integrated Data Analysis System
MRP	Mutual Recognition Procedure
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
OA	osteoarthritis
OR	odds ratio
PBRER	Periodic Benefit-Risk Evaluation Report
PFS	progression-free survival
PHR	partial hip replacement
PL	Package Leaflet
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
QPPV	Qualified Person for Pharmacovigilance
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(ly)
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 7.3 MedDRA Search Strategy for Important Risks**

The following MedDRA terms were used in the database search for each important identified risk and important potential risk presented in the tables in Section SVII.3.

Pure red cell aplasia:

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.

Disease progression:

Condition aggravated, disease progression, malignant neoplasm progression, neoplasm progression

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

<b>Version Number</b>	<b>Approval Date Procedure</b>	<b>Change</b>
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 FR/H/0003/009-010, 013-014/II/129	Draft versions:  5.1: Added new important potential risks: Seizures and Hypersensitivity/Anaphylaxis; updated important identified risk of Hypertension to Hypertension/Hypertensive crisis  5.3: Risks of Seizures and Hypersensitivity/Anaphylaxis moved from important potential risks to important identified risks.  Outcome: - Updated important identified risk of Hypertension to Hypertension/Hypertensive crisis. - Seizures and Hypersensitivity/Anaphylaxis were not maintained as important identified risks.
6.0 Succession 2	FR/H/0003/009-010, 013-014/II/132  28 March 2019 (MRP End of Procedure)	Draft versions:  5.2: Updated with data from clinical study report (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 anaemic 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, 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.

Version Number	Approval Date Procedure	Change
		<p>6.0 Succession 1:</p> <p>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).</p> <p>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.</p>
7.1	Working version replaced by Version 7.2.	<p>Document updated to remove annual immunogenicity reports and ISAC adjudication from the list of routine pharmacovigilance activities beyond adverse reaction reporting and signal detection, in line with the ANSM conclusions regarding the assessment of the 17th and 18th immunogenicity reports (second and third annual immunogenicity reports, respectively).</p> <p>Bulgaria and Ireland were removed from the list of MAHs (EPREX/ERYPO licenses withdrawn), postmarketing data were updated to align with PBRER with data lock point 31 August 2021, and the RMP was aligned with the latest approved EU-MRP Product Information.</p> <p>Editorial changes made throughout to align with the latest company RMP template.</p> <p><u>Pharmacovigilance Plan</u></p> <p>Removal of annual immunogenicity reports and ISAC adjudication from the list of routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.</p>
7.2	FR/H/xxxx/WS/282 10 October 2022 (MRP End of Procedure)	<p>Final for Procedure FR/H/xxxx/WS/282. Health Authority approval date 10 October 2022</p> <p>Implementation of minor changes requested by the French Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) further to the review of EU-RMP Version 7.1, namely clarification that the second and third annual immunogenicity reports were the 17th and 18th reports overall, clarification that a statement on comorbidities in pediatric patients was specific to pediatric patients with CRF, and correction of a formatting error in Part VI.II.B.</p> <p>Finland and Norway were removed from the list of MAHs (EPREX/ERYPO licenses withdrawn).</p>

# Signature

User	Date	Reason
[REDACTED]	18-Oct-2022 08:35:37 (GMT)	Document Approval