ERYSAA® PREFILLED SYRINGE

Epoetin alfa

DESCRIPTION

ERYSAA® PREFILLED SYRINGE 2,000 IU/0.5ml is a sterile, clear, colorless liquid in phosphate-buffered solution for intravenous administration that is available in single-use, graduated pre-filled syringes containing 2,000 IU/0.5ml.

ERYSAA® PREFILLED SYRINGE 4,000 IU/0.4ml is a sterile, clear, colorless liquid in phosphate-buffered solution for intravenous administration that is available in single-use, graduated pre-filled syringes containing 4,000 IU/0.4ml.

ERYSAA® PREFILLED SYRINGE 6,000 IU/0.6ml is a sterile, clear, colorless liquid in phosphate-buffered solution for intravenous administration that is available in single-use, graduated pre-filled syringes containing 6,000 IU/0.6ml.

ERYSAA® PREFILLED SYRINGE 10,000 IU/1.0ml is a sterile, clear, colorless liquid in phosphate-buffered solution for intravenous administration that is available in single-use, graduated pre-filled syringes containing 10,000 IU/1.0ml.

COMPOSITION

ERYSAA® PREFILLED SYRINGE 2,000IU/0.5ml: Each pre-filled syringe contains Epoetin alfa 2,000 international units (IU) corresponding to 16.8 micrograms Epoetin alfa.

ERYSAA® PREFILLED SYRINGE 4,000IU/0.4ml: Each pre-filled syringe contains Epoetin alfa 4,000 international units (IU) corresponding to 33.6 micrograms Epoetin alfa.

ERYSAA® PREFILLED SYRINGE 6,000IU/0.6ml: Each pre-filled syringe contains Epoetin alfa 6,000 international units (IU) corresponding to 50.4 micrograms Epoetin alfa.

ERYSAA® PREFILLED SYRINGE 10,000IU/1.0ml: Each pre-filled syringe contains Epoetin alfa 10,000 international units (IU) corresponding to 84.0 micrograms Epoetin alfa.

Epoetin alfa is a glycoprotein that is produced by recombinant DNA technology.

ERYSAA® is a biosimilar to Eprex®.

PHARMACODYNAMICS

ERYSAA® stimulates erythropoiesis by the same mechanism as endogenous erythropoietin.

ERYSAA® (Epoetin alfa) obtained by gene technology is glycosylated and is identical in its amino acid and carbohydrate composition to endogenous human erythropoietin that has been isolated from the urine of anaemic patients.

ERYSAA® has the highest possible purity according to the latest state of the art technology. In particular, no residues of the cell line used for the production are detectable at the concentrations of the active ingredient that are used in humans.

Healthy volunteers

After single I.V. bolus (100 IU/kg) of ERYSAA®, the pharmacodynamic marker reticulocyte was investigated. ERYSAA® increases the reticulocyte count within 7 days of initiation as similar to the pharmacodynamic profile of reference medicinal product Eprex®.

Phase I study (PG-EPO-Ph1) in healthy subjects provided comparative pharmacodynamic data on ERYSAA® versus Eprex®. For 27 subjects who completed the study per protocol, the blood levels of RBC, haemoglobin, haematocrit and reticulocyte were determined up to 28 days following single-dose intravenous administration of Eprex® or ERYSAA® at an IV bolus dose of 100 IU/kg. The key PD parameters of absolute reticulocyte count were calculated as follows: median T_{max} was 7 days for both Eprex® and ERYSAA®. E_{max} was 95.4(±21.7) × 10^3/μL and 93.4(±24.2) × 10^3/μL for Eprex® and ERYSAA®, respectively and $AUEC_{last}$ was 1773.6(±404.0) × 10^3/μL × day and 1832.6(±414.4) ×10^3/μL × day for Eprex® and ERYSAA®, respectively. The point-estimates and 90% CIs for both E_{max} GMR (test/reference) and $AUEC_{last}$ GMR (test/reference) lie within the equivalence margin of 0.8~1.25 and thus fulfill the criteria for PD comparability between ERYSAA® and Eprex®.

The following data for the pharmacodynamics in chronic renal failure patients administered with epoetin alfa is summarized from publicly available information from Eprex®

Epoetin alfa (Eprex®) has been shown to stimulate erythropoiesis in anaemic patients with CRF, including dialysis and pre-dialysis patients. The first evidence of a response to epoetin alfa is an increase in the reticulocyte count within 10 days, followed by increases in the red cell count, haemoglobin and haematocrit, usually within 2 to 6 weeks. The haemoglobin response varies between patients and may be impacted by iron stores and the presence of concurrent medical problems.

The following data for the pharmacodynamics in patients with adult surgery patients in an autologous predonation programme administered with epoetin alfa is summarized from publicly available information from Eprex®

Epoetin alfa (Eprex®) has been shown to stimulate red blood cell production in order to augment autologous blood collection, and to limit the decline in haemoglobin in adult patients scheduled for major elective surgery who are not expected to predeposit their complete perioperative blood needs. The greatest effects are observed in patients with low haemoglobin (≤ 13 g/dL).

PHARMACOKINETICS

Healthy volunteers

After single I.V. bolus (100 IU/kg) of ERYSAA® was observed for their plasma erythropoietin concentrations determined up to 24 hours. Measurement of epoetin alfa following single dose intravenous administration revealed a half-life of approximately 7 hours in normal volunteers.

A Phase I study (PG-EPO-Ph1) in healthy subjects provided pharmacokinetic (PK) data on ERYSAA® in comparison to Eprex®. In that study, 27 individual subjects completed the study per protocol and had their plasma erythropoietin concentrations determined up to 24 hours following single-dose intravenous administration of Eprex® or ERYSAA® at an IV bolus dose

of 100 IU/kg. The key PK parameters of plasma erythropoietin concentration were calculated as follows: T_{max} was 0.083 hours for both Eprex® and ERYSAA® treatment groups. C_{max} was 2518.50(±269.30) mIU/mL and 2531.21(±272.50) mIU/mL for Eprex® and ERYSAA®, respectively, and AUC_{last} was 17094.51(±2141.31) hr × mIU/mL, and 16464.51(±1872.40) hr × mIU/mL for Eprex® and ERYSAA®, respectively. In addition, respective CL values for Eprex® and ERYSAA® were 0.41(±0.06) L/hr and 0.42(±0.04) L/hr. The point estimates and 90% CIs for both C_{max} geometric mean ratio (GMR) (test/reference) and AUC_{last} GMR (test/reference) lie within the equivalence margin of 0.8~1.25 and thus fulfill the criteria for PK comparability between ERYSAA® and Eprex®.

The following data for the pharmacokinetics in healthy volunteers administered with epoetin alfa is summarized from publicly available information from Eprex®

The mean volume of distribution was 49.3 mL/kg after intravenous doses of 50 and 100 IU/kg in healthy subjects. Following intravenous administration of epoetin alfa in subjects with chronic renal failure, the volume of distribution ranged from 57-107 mL/kg after single dosing (12 IU/kg) to 42-64 mL/kg after multiple dosing (48-192 IU/kg), respectively. Thus, the volume of distribution is slightly greater than the plasma space.

The half-life of epoetin alfa following multiple dose intravenous administration is approximately 4 hours in healthy subjects.

In healthy subjects, a dose-proportional increase in serum epoetin alfa concentrations was observed after intravenous administration of 150 and 300 IU/kg, 3 times per week.

In studies to explore extending the dosing interval (40,000 IU once weekly and 80,000, 100,000, and 120,000 IU biweekly), a linear but non-dose-proportional relationship was observed between mean C_{max} and dose, and between mean AUC and dose at steady state.

Epoetin alfa exhibits a dose-related effect on haematological parameters which is independent of route of administration.

The following data for the pharmacokinetics in paediatric population administered with epoetin alfa is summarized from publicly available information from Eprex®

A half-life of approximately 6.2 to 8.7 hours has been reported in paediatric subjects with chronic renal failure following multiple dose intravenous administration of epoetin alfa (Eprex®). The pharmacokinetic profile of epoetin alfa in children and adolescents appears to be similar to that of adults.

Pharmacokinetic data in neonates is limited.

A study of 7 preterm very low birth weight neonates and 10 healthy adults given i.v. erythropoietin suggested that distribution volume was approximately 1.5 to 2 times higher in the preterm neonates than in the healthy adults, and clearance was approximately 3 times higher in the preterm neonates than in healthy adults.

The following data for the pharmacokinetics in chronic renal failure patients administered with epoetin alfa is summarized from publicly available information from Eprex®

In chronic renal failure patients, the half-life of intravenously administered epoetin alfa Eprex® is slightly prolonged, approximately 5 hours, compared to healthy subjects.

CLINICAL TRIALS

The multi-center, multi-national, double-blind, randomized, active controlled, parallel-group Phase III study (PG-EPO-Ph3) was conducted in a total of 298 Malaysian and Korean subjects where both populations were exposed to treatment of the product. The 2,000 IU/0.5ml strength was tested during the study and showed therapeutic equivalence with the reference product Eprex® so similar clinical effect can be expected on the hemoglobin levels of patients. The study design also includes exposure to the ERYSAA® of up to 12-months during the open label phase to assess the long-term immunogenicity safety (see ADVERSE EFFECTS/UNDESIRABLE EFFECTS).

The following data for the clinical efficacy and safety in chronic renal failure patients administered with epoetin alfa is summarized from publicly available information from Eprex®

Epoetin alfa (Eprex®) has been studied in clinical trials in adult anaemic CRF patients, including haemodialysis and pre-dialysis patients, to treat anaemia and maintain haematocrit within a target concentration range of 30 to 36%. In clinical trials at starting doses of 50 to 150 IU/kg, three times per week, approximately 95% of all patients responded with a clinically significant increase in haematocrit. After approximately two months of therapy, virtually all patients were transfusion-independent. Once the target haematocrit was achieved, the maintenance dose was individualised for each patient.

In the three largest clinical trials conducted in adult patients on dialysis, the median maintenance dose necessary to maintain the haematocrit between 30 to 36% was approximately 75 IU/kg given 3 times per week.

In a double-blind, placebo-controlled, multicentre, quality of life study in CRF patients on haemodialysis, clinically and statistically significant improvement was shown in the patients treated with epoetin alfa compared to the placebo group when measuring fatigue, physical symptoms, relationships and depression (Kidney Disease Questionnaire) after six months of therapy. Patients from the group treated with epoetin alfa were also enrolled in an open-label extension study which demonstrated improvements in their quality of life that were maintained for an additional 12 months.

Epoetin alfa (Eprex®) was evaluated in an open-label, non-randomised, open dose-range, 52-week clinical study in paediatric CRF patients undergoing haemodialysis. The median age of patients enrolled in the study was 11.6 years (range 0.5 to 20.1 years). Epoetin alfa was administered at 75 IU/kg/week intravenously in 2 or 3 divided doses post-dialysis, titrated by 75 IU/kg/week at intervals of 4 weeks (up to a maximum of 300 IU/kg/week), to achieve a 1 g/dL/month increase in haemoglobin. The desired haemoglobin concentration range was 9.6 to 11.2 g/dL. Eighty-one percent of patients achieved the haemoglobin concentration level. The median time to target was 11 weeks and the median dose at target was 150 IU/kg/week. Of the patients who achieved the target, 90% did so on a 3-times-per-week dosing regimen.

After 52 weeks, 57% of patients remained in the study, receiving a median dose of 200 IU/kg/week.

The following data for the clinical efficacy and safety in adult patients with renal insufficiency not yet undergoing dialysis administered with epoetin alfa is summarized from publicly available information from Eprex®

In clinical trials conducted in patients with CRF not on dialysis treated with epoetin alfa (Eprex®), the average duration of therapy was nearly five months. These patients responded to epoetin alfa therapy in a manner similar to that observed in patients on dialysis. Patients with CRF not on dialysis demonstrated a dose-dependent and sustained increase in haematocrit when epoetin alfa was administered by intravenous route. Similar rates of rise of haematocrit were noted when epoetin alfa was administered by either route. Moreover, epoetin alfa doses of 75 to 150 IU/kg per week have been shown to maintain haematocrits of 36 to 38% for up to six months.

In 2 studies with extended interval dosing of Eprex® (3 times per week, once weekly, once every 2 weeks, and once every 4 weeks) some patients with longer dosing intervals did not maintain adequate haemoglobin levels and reached protocol-defined haemoglobin withdrawal criteria (0% in once weekly, 3.7% in once-every-2-weeks, and 3.3% in the once-every-4-weeks groups).

A randomized prospective trial (CHOIR) evaluated 1,432 anaemic chronic renal failure patients who were not undergoing dialysis. Patients were assigned to epoetin alfa treatment targeting a maintenance haemoglobin level of 13.5 g/dL (higher than the recommended haemoglobin concentration level) or 11.3 g/dL. A major cardiovascular event (death, myocardial infarction, stroke or hospitalization for congestive heart failure) occurred among 125 (18%) of the 715 patients in the higher haemoglobin group compared to 97 (14%) among the 717 patients in the lower haemoglobin group (hazard ratio [HR] 1.3, 95% CI: 1.0, 1.7, p = 0.03).

Pooled post-hoc analyses of clinical studies of ESAs have been performed in chronic renal failure patients (on dialysis, not on dialysis, in diabetic and non-diabetic patients). A tendency towards increased risk estimates for all-cause mortality, cardiovascular and cerebrovascular events associated with higher cumulative ESA doses independent of the diabetes or dialysis status was observed.

The following data for the clinical efficacy and safety in adult surgery patients in an autologous predonation programme administered with epoetin alfa is summarized from publicly available information from Eprex®

The effect of epoetin alfa (Eprex®) in facilitating autologous blood donation in patients with low haematocrits (≤ 39% and no underlying anaemia due to iron deficiency) scheduled for major orthopaedic surgery was evaluated in a double-blind, placebo-controlled study conducted in 204 patients, and a single-blind placebo controlled study in 55 patients.

In the double-blind study, patients were treated with epoetin alfa 600 IU/kg or placebo intravenously once daily every 3 to 4 days over 3 weeks (total 6 doses). On average, patients

treated with epoetin alfa were able to predeposit significantly more units of blood (4.5 units) than placebo-treated patients (3.0 units).

In the single-blind study, patients were treated with epoetin alfa 300 IU/kg or 600 IU/kg or placebo intravenously once daily every 3 to 4 days over 3 weeks (total 6 doses). Patients treated with epoetin alfa were also able to predeposit significantly more units of blood (epoetin alfa 300 IU/kg = 4.4 units; epoetin alfa 600 IU/kg = 4.7 units) than placebo-treated patients (2.9 units).

Epoetin alfa therapy reduced the risk of exposure to allogeneic blood by 50% compared to patients not receiving epoetin alfa.

INDICATION

ERYSAA® is an erythropoiesis-stimulating agent (ESA) indicated for:

i. Treatment of anaemia associated with chronic renal failure in adult haemodialysis and predialysis patients and paediatric patients on haemodialysis.
ii. To facilitate autologous blood collection within a predeposit program and decrease the risk of receiving allogeneic blood transfusions in patients with hematocrits of 33 - 39%, who are scheduled for major elective surgery and are expected to require more blood than that which can be obtained through autologous blood collection techniques in the absence of Epoetin alfa.

RECOMMENDED DOSAGE

Adult haemodialysis patients

In patients on haemodialysis, where intravenous access is readily available, the intravenous route of administration should be used for ERYSAA®.

The treatment is divided into two stages:

Correction phase: 50 IU/kg three times per week. When necessary, dose adjustments should be made in increments of 25 IU/kg three times per week at intervals of at least 4 weeks until the target haemoglobin concentration (10-12 g/dL) is achieved.

Maintenance phase: Adjust dosage in order to maintain haemoglobin values at the desired level: Hb between 10 and 12 g/dL. The maintenance dose should be individualised for each chronic renal failure patient. The recommended total weekly dose is between 75 and 300 IU/kg. Available data suggests that patients with a baseline haemoglobin (<6 g/dL) may require higher maintenance doses than patients with a baseline haemoglobin (>8 g/dL).

Paediatric Haemodialysis Patients

The treatment is divided into two stages:

Correction phase: 50 IU/kg three times per week by the intravenous route. When necessary, dose adjustments should be made in increments of 25 IU/kg three times per week at intervals of at least 4 weeks until the target haemoglobin concentration (9.5-11 g/dL) is achieved.

Maintenance phase: Adjust dosage in order to maintain haemoglobin values at the desired level: Hb between 9.5-11 g/dL. Generally, children less than 30 kg require higher maintenance doses than children over 30 kg and adults. For example, the following maintenance doses were observed in clinical trials after 6 months of treatment.

Dose (IU/kg given 3x/week)		
Weight (kg)	Median	Usual Maintenance Dose
<10	100	75 – 100
10 – 30	75	60 – 150
>30	33	30 – 100

Available data suggest that patients whose initial haemoglobin is very low (haemoglobin <6.8 g/dL) may require higher maintenance doses than patients whose initial haemoglobin is higher (haemoglobin 6.8 g/dL).

Adult surgery patients in an autologous predonation programme

The intravenous route of administration should be used for ERYSAA®. Epoetin alfa should be administered after the completion of each blood donation procedure. Iron status should be evaluated for all patients prior to treatment with Epoetin alfa. Iron deficiency, if present, should be corrected before allowing a patient to enroll in an autologous blood donation programme. In anemic patients, the cause of anaemia should be explored before starting therapy with Epoetin alfa. All patients being treated with Epoetin alfa should receive adequate iron supplementation (e.g. 200 mg oral elemental iron daily) throughout the course of Epoetin alfa treatment. In order to achieve high iron stores prior to starting Epoetin alfa therapy, iron supplementation should be started as soon as possible, even several weeks prior to initiating the autologous pre-deposit. Mildly anaemic patients (haematocrit of 33 to 39% and/or haemoglobin 10 to 13 g/dL), requiring predeposit of ≥ 4 units of blood, should be treated with Epoetin alfa at 600 IU/kg 2 times weekly for 3 weeks prior to surgery. For those patients who require a lesser degree of erythropoietin stimulation, a dose regimen of 150-300 IU/kg administered twice weekly has been shown to augment autologous predonation and to decrease the subsequent decline in haematocrit.

ROUTE OF ADMINISTRATION

ERYSAA® is preservative free sterile solution for single use only.

This medicinal product must not be administered by intravenous infusion, or mixed with other medicinal products.

This medicinal product is not approved for subcutaneous use.

Intravenous injection:

Epoetin alfa should be administered over at least one to five minutes, depending on the total dose. A slower injection may be preferable in patients who react to the treatment with flu-like symptoms. In haemodialysis patients, a bolus injection may be given during dialysis via a suitable venous port in the dialysis line. Alternatively, at the completion of a haemodialysis session, the injection can be given via the fistula needle tubing, followed by 10 ml of isotonic

saline to rinse the tubing and to ensure satisfactory injection of the product into the circulation. Epoetin alfa should not be administered by intravenous infusion or mixed with other drugs.

Special instruction for use

The pre-filled syringe is ready for use. Each syringe should be used for a single injection only. Do not re-use syringe. Discard unused portion. ERYSAA® must not be shaken or mixed with any other liquid. Shaking may denature the glycoprotein, rendering it inactive.

Do not use ERYSAA® if:

- the blister sealing is broken or the blister is damaged in any way
- the liquid is coloured or you can see particles floating in it
- any liquid has leaked out of the pre-filled syringe or condensation is visible within the sealed blister
- you know or think it may have been accidentally frozen

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Hypersensitivity to mammalian cell- derived products
- Uncontrolled hypertension
- Patients who develop antibody-mediated Pure Red Cell Aplasia (PRCA) following treatment with any erythropoietin should not receive Epoetin alfa or any other erythropoietin
- All contraindications associated with autologous blood predonation programs should be respected in patients being supplemented with ESA.
- Patients scheduled for elective surgery, who are not participating in an autologous blood pre-deposit programme and who have severe coronary, peripheral arterial, carotid or cerebral vascular disease, including patients with recent myocardial infarction or cerebral vascular accident.
- Surgery Patients who for any reason cannot receive adequate antithrombotic prophylaxis or treatment.

WARNINGS AND PRECAUTIONS

Cardiovascular and Thrombotic Events/Increased Mortality

An increased incidence of thrombotic vascular events (TVEs) has been observed in patients receiving epoetin alfa. These include venous and arterial thromboses and embolism (including some with fatal outcomes), such as deep venous thrombosis, pulmonary emboli, retinal thrombosis and myocardial infarction. Additionally, cerebrovascular accidents (including cerebral infarction, cerebral haemorrhage and transient ischaemic attacks) have been reported.

The reported risk of TVEs should be carefully weighed against the benefits to be derived from treatment with epoetin alfa particularly in patients with pre-existing risk factors. In all patients, haemoglobin levels should be closely monitored due to a potential increased risk of thromboembolic events and fatal outcomes when patients are treated at haemoglobin levels above the target for the indication of use.

Use in Chronic Renal Failure Patients

Chronic renal failure patients being treated with epoetin alfa should have haemoglobin levels measured on a regular basis until a stable level is achieved, and periodically thereafter. In chronic renal failure patients the rate of increase in haemoglobin should be approximately 1 g/dL per month and should not exceed 2 g/dL per month to minimise risks of an increase in hypertension.

In patients with chronic renal failure, maintenance haemoglobin concentration should not exceed the upper limit of the target haemoglobin concentration range as recommended under Recommended Dosage. In controlled trials, haemoglobin levels targeted to 13 g/dL were associated with a higher risk of cardiovascular events, including death.

Patients with chronic renal failure and insufficient haemogloblin response to ESA therapy may be at even greater risk for cardiovascular events and mortality than other patients. Shunt thromboses have occurred in haemodialysis patients, especially in those who have a tendency to hypotension or whose arteriovenous fistulae exhibit complications (e.g., stenoses, aneurysms, etc.) Early shunt revision and thrombosis prophylaxis by administration of acetylsalicylic acid, for example, is recommended in these patients.

Hyperkalaemia has been observed in isolated cases. Serum electrolytes should be monitored in chronic renal failure patients. If an elevated or rising serum potassium level is detected, then in addition to the appropriate treatment of the hyperkalaemia, consideration should be given to ceasing ESA administration until the serum potassium level has been corrected.

Hypertension

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

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

Pure Red Cell Aplasia

Cases of pure red cell aplasia (PRCA) have been reported after months to years of treatment with erythropoietins. Most cases of PRCA associated with ESA occurred in patients receiving subcutaneous (SC) administration. Cases also have been reported in patients with hepatitis C treated with interferon and ribavirin, when ESAs are used concomitantly. ESAs are not approved in the management of anaemia associated with hepatitis C.

In patients developing sudden lack of efficacy typical causes of non-response should be investigated. If no cause is identified, a bone marrow examination should be considered. If

antibodies to erythropoietin are detected, patients should not be switched to another ESA product as anti-erythropoietin antibodies cross-react with other ESAs.

Use in Surgery Patients in an Autologous Pre-Donation Programme (ABD)

All special precautions associated with autologous pre-donation programmes, especially routine volume replacement, should be respected.

Seizures

Seizures have occurred in patients receiving ESA. Therefore, ESA should be used with caution in patients with epilepsy, history of seizures, or medical conditions associated with a predisposition to seizure activity such as CNS infections and brain metastases.

Sensitivity/ Resistance

The parenteral administration of any biologic product should be attended by appropriate precautions in case allergic or other untoward reactions occur. Hypersensitivity reactions, including cases of rash, urticaria, anaphylactic reaction, and angioneurotic edema have been reported.

Severe Cutaneous Adverse Reactions

Blistering and skin exfoliation reactions including erythema multiforme and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), have been reported in association with ESA treatment. Discontinue ESA therapy immediately if a severe cutaneous adverse reaction, such as SJS/TEN, is suspected.

Iron Supplementation

Other causes of anaemia (iron, folate or Vitamin B12 deficiency, aluminium intoxication, infection or inflammation, blood loss, haemolysis and bone marrow fibrosis of any origin) should be evaluated and treated prior to initiating therapy with ESA, and when deciding to increase the dose. In most cases, the ferritin values in the serum fall simultaneously with the rise in packed cell volume. In order to ensure optimum response to ESA, adequate iron stores should be assured and iron supplementation should be administered if necessary:

- For chronic renal failure patients, iron supplementation (elemental iron 200-300 mg/day orally for adults and 100-200 mg/day orally for paediatrics) is recommended if serum ferritin levels are below 100 ng/mL.
- For cancer patients, iron supplementation (elemental iron 200-300 mg/day orally) is recommended if transferring saturation is below 20%.
- For patients in an autologous predonation programme, iron supplementation (elemental iron 200 mg/day orally) should be administered several weeks prior to initiating the autologous predeposit in order to achieve high iron stores prior to starting ESA therapy, and throughout the course of ESA therapy.

General

There may be a moderate dose-dependent rise in the platelet count within the normal range during treatment with ESA. This regresses during the course of continued therapy. In addition, thrombocythaemia above the normal range has been reported. It is recommended that the platelet count is regularly monitored during the first 8 weeks of therapy.

Very rarely, exacerbation of porphyria has been observed in ESA-treated patients. ESAs should be used with caution in patients with known porphyria.

ESA should also be used with caution in patients with chronic liver failure. The safety and dosage regime of ESA has not been established in the presence of hepatic dysfunction.

Patients should only be switched from one ESA to another under appropriate supervision.

Effect on Ability to Drive and Operate Machinery

No studies on the effects of epoetin alfa on the ability to drive and use machines have been performed.

INTERACTIONS WITH OTHER MEDICAMENTS

No evidence of interaction of epoetin with other drugs was observed in the course of clinical trials. However, since cyclosporine is bound by RBCs there is potential for a drug interaction. If epoetin alfa is given concomitantly with cyclosporine, blood levels of cyclosporine should be monitored and the dose of cyclosporine adjusted as the haematocrit rises.

PREGNANCY AND LACTATION

There are no adequate and well-controlled studies with epoetin alfa in pregnant women. ESA should be administered during pregnancy only if clearly needed and if the potential benefit justifies the potential risk to the foetus. In pregnant or lactating surgical patients participating in an autologous blood predonation programme, the use of ESA is not recommended. It is not known whether epoetin alfa (rch) is excreted in breast milk.

ADVERSE EFFECTS/ UNDESIRABLE EFFECTS

To determine long term safety, the TEAEs that had occurred in 274 subjects administered at least one dose of PDA10 in the entire study period including the OLE phase were evaluated and the numbers of TEAEs per patient year were analyzed. In addition to this, the numbers of TEAEs per patient year for 146 subjects in the Eprex® group during the maintenance phase was also presented as a reference.

The adverse events (AEs) that had occurred in the entire study period were summarized by System Organ Class (SOC) and Preferred Term (PT) and their tabulated summary (≥ 2% of incidence rate by PT) is provided in Table 1 below.

The incidence of TEAEs per exposure year was similar between the groups treated with PDA10 and Eprex®. Among 274 subjects in the PDA10 group who had received at least one dose of PDA10 in the entire study period including the OLE phase, 169 subjects (61.68% [613 events; 3.22 events per patient year]) had at least one TEAE during the entire study period.

By system organ class (SOC), the most common TEAE in the PDA10 group was 'Infections and infestations' with 119 events reported by 74 subjects (27.01% [0.63 events per patient year]), followed by 'Injury, poisoning and procedural complications' with 68 events reported by 46 subjects (16.79% [0.36 events per patient year]). By PT, the most common TEAE was 'Hypertension' with 71 events reported by 21 subjects (7.66% [0.37 events per patient year]), followed by 'Nasopharyngitis' with 32 events reported by 20 subjects (7.30% [0.17 events per patient year]). Adverse events (AEs) were summarized by System Organ Class (SOC) and Preferred Term (PT) and their tabulated summary is provided in Table.

Table 1. Incidences of TEAEs by SOC and PT (≥ 2% incidence by PT)

	ERYSAA® (N=274)	**Eprex® (N=146)**
Subjects with TEAEs	61.68	60.27
Infections and infestations	27.01	23.29
Upper respiratory tract infection	6.20	7.53
Nasopharyngitis	7.30	4.79
Pneumonia	3.28	2.05
Arteriovenous fistula site infection	2.19	0.68
Gastrointestinal disorders	16.42	16.44
Diarrhoea	4.38	2.74
Constipation	1.46	2.74
Gastritis	2.19	0
Abdominal pain upper	0.73	2.05
Upper gastrointestinal haemorrhage	0	2.05
Injury, poisoning and procedural complications	16.79	14.38
Procedural hypotension	5.11	2.74
Arteriovenous fistula site complication	2.55	2.05
Arteriovenous fistula thrombosis	0.36	3.42
Metabolism and nutrition disorders	10.95	8.90
Fluid overload	2.92	2.74
Hyperkalaemia	0.73	2.74
Vascular disorders	10.95	8.90
Hypertension	7.66	6.16
General disorders and administration site conditions	10.22	8.22
Pyrexia	2.92	2.74
Nervous system disorders	9.85	7.53
Dizziness	2.55	3.42
Musculoskeletal and connective tissue disorders	8.76	8.22
Muscle spasms	2.92	2.74
Respiratory, thoracic and mediastinal disorders	6.93	8.90
Cough	1.82	2.05
Rhinorrhoea	0.36	2.05
Surgical and medical procedures	1.82	2.05
Renal transplant	0.36	2.05

TEAEs = Treatment-Emergent Adverse Events, SOC = system organ class, PT = preferred term. MedDRA

The adverse drug reactions (ADRs), were 10 events reported by 5 subjects (1.69%) including 6 events by 3 subjects (2.00%) in the ERYSAA® group and 4 events by 2 subjects (1.37%) in the Eprex® group.

By SOC, the most common ADR in the PDA10 group was 'Vascular disorders' with 39 events reported by 3 subjects (1.09% [0.21 events per patient year]), followed by 'Nervous system disorders' with 2 events reported by 2 subjects (0.73% [0.01 events per patient year]) and 'Skin and subcutaneous tissue disorders' with 1 event reported by 1 subject (0.36% [0.01 event per patient year]). By PT, the most common ADR was 'Hypertension' with 37 events reported by 2 subjects (0.73% [0.19 events per patient year]), followed by 'Blood pressure inadequately controlled', 'Hypertensive crisis', 'Cerebral infarction', 'Haemorrhage intracranial' and 'Rash' with 1 event reported by 1 subject each (0.36% [0.01 event per patient year]). The ADRs reported during the entire study are presented by SOC and PT in Table 2.

Table 2. Incidence of ADRs by SOC and PT

	ERYSAA® (N=274)	**Eprex® (N=146)**
Subjects with ADRs	1.82	1.37
Vascular disorders	1.09	1.37
Hypertension	0.73	1.37
Blood pressure inadequately controlled	0.36	0
Hypertensive crisis	0.36	0
Nervous system disorders	0.73	0
Cerebral infarction	0.36	0
Haemorrhage intracranial	0.36	0
Skin and subcutaneous tissue disorders	0.36	0
Rash	0.36	0

ADRs= Adverse Drug Reactions, SOC= system organ class, PT= preferred term. MedDRA version: 19.0.

The following safety profile is summarized from publicly available information from Eprex®

Summary of Safety Profile

The most frequent adverse drug reaction during treatment with epoetin alfa is a dose-dependent increase in blood pressure or aggravation of existing hypertension. Monitoring of the blood pressure should be performed, particularly at the start of therapy (see WARNINGS AND PRECAUTIONS).

The most frequently occurring adverse drug reactions observed in clinical trials of epoetin alfa are diarrhoea, nausea, vomiting, pyrexia and headache. Influenza-like illness may occur especially at the start of treatment.

Respiratory tract congestion, which includes events of upper respiratory tract congestion, nasal congestion and nasopharyngitis, have been reported in studies with extended interval dosing in adult patients with renal insufficiency not yet undergoing dialysis.

An increased incidence of thrombotic vascular events (TVEs) has been observed in patients receiving ESAs (see WARNINGS AND PRECAUTIONS).

Tabulated List of Adverse Reactions

Of a total 3,417 subjects in 25 randomized, double-blinded, placebo or standard of care controlled studies, the overall safety profile of Eprex® was evaluated in 2,094 anaemic subjects. Included were 228 epoetin alfa-treated CRF subjects in 4 chronic renal failure studies (2 studies in predialysis [N = 131 exposed CRF subjects] and 2 in dialysis [N = 97 exposed CRF subjects]; 1,404 exposed cancer subjects in 16 studies of anaemia due to chemotherapy; 147 exposed subjects in 2 studies for autologous blood donation; 213 exposed subjects in 1 study in the perisurgical period, and 102 exposed subjects in 2 myelodysplastic syndromes (MDS) studies. Adverse drug reactions reported by ≥1% of subjects treated with epoetin alfa in these trials are shown in the table below.

Frequency estimate: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very Rare (< 1/10,000), Not known (cannot be estimated from the available data).

MedDRA System Organ Classification (SOC)	**Adverse Reaction (Preferred Term Level)**	**Frequency**
Blood and lymphatic system disorders	Pure red cell aplasia[3], Thrombocythemia	Rare
Metabolism and nutrition disorders	Hyperkalaemia[1]	Uncommon
Immune system disorders	Hypersensitivity[3]	Uncommon
	Anaphylactic reaction[3]	Rare
Nervous system disorders	Headache	Common
	Convulsion	Uncommon
Vascular disorders	Hypertension, Venous and arterial thromboses[2]	Common
	Hypertensive crisis[3]	Not known
Respiratory, thoracic and mediastinal disorders	Cough	Common
	Respiratory tract congestion	Uncommon
Gastrointestinal disorders	Diarrhoea, Nausea, Vomiting	Very common
Skin and subcutaneous tissue disorders	Rash	Common
	Urticaria[3]	Uncommon
	Angioneurotic oedema[3]	Not known
Musculoskeletal and connective tissue disorders	Arthralgia, Bone pain, Myalgia, Pain in extremity	Common
Congenital, familial and	Porphyria acute[3]	Rare

genetic disorders		
General disorders and administration site conditions	Pyrexia	Very common
	Chills, Influenza like illness, Injection site reaction, Oedema peripheral	Common
	Drug ineffective[3]	Not known
Investigations	Anti-erythropoeitin antibody positive	Rare

[1] Common in dialysis
[2] Includes arterial and venous, fatal and non fatal events, such as deep venous thrombosis, pulmonary emboli, retinal thrombosis, arterial thrombosis (including myocardial infarction), cerebrovascular accidents (including cerebral infarction and cerebral haemorrhage) transient ischaemic attacks, and shunt thrombosis (including dialysis equipment) and thrombosis within arteriovenous shunt aneurisms
[3] Addressed in WARNINGS AND PRECAUTIONS

Description of selected adverse reactions

Hypersensitivity reactions, including cases of rash (including urticaria), anaphylactic reactions, and angioneurotic oedema have been reported.

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

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with epoetin treatment (see WARNINGS AND PRECAUTIONS).

Antibody-mediated pure red cell aplasia has been very rarely reported in < 1/10,000 cases per patient year after months to years of treatment with Eprex®.

Paediatric population with chronic renal failure on haemodialysis

The exposure of paediatric patients with chronic renal failure on haemodialysis in clinical trials and post-marketing experience is limited. No paediatric-specific adverse reactions not mentioned previously in the table above, or any that were not consistent with the underlying disease were reported in this population.

OVERDOSE AND TREATMENT

The therapeutic margin of Epoetin alfa is very wide. Overdose of epoetin alfa may produce effects that are extensions of the pharmacological effects of the hormone. Phlebotomy may be performed if excessively high haemoglobin levels occur. Additional supportive care should be provided as necessary.

Preclinical Safety Data
Single Dose Toxicity

No single dose toxicity studies were performed. According to literature data, the highest epoetin alfa dose tested was > 40 times the highest human dose administered clinical today (600 IU/kg).

Repeated Dose Toxicity

In accordance with the guidelines on the evaluation of biosimilar products, a repeat-dose toxicity study with 2-week recovery was conducted in one animal species with 2 different dosages (100 IU/kg and 500 IU/kg) administered daily for 28 days to examine and compare the safety of study drug ERYSAA® and comparator drug Eprex®. The results demonstrated that two drugs were not different in terms of toxicity. And during the test period, no death occurred in either males or females.

INCOMPATIBILITIES

Do not dilute or transfer to any other container. Do not administer by intravenous infusion or in conjunction with other drug solutions.

STORAGE CONDITIONS

Store at (2°C ~ 8°C). Do not freeze or shake. Shaking may denature the glycoprotein, rendering it inactive.

Protect from light. Keep the pre-filled syringes in the original carton. When the product is about to be used, it may be removed from the refrigerator and stored at room temperature (below 25°C) for a maximum single period of seven days.

Keep out of reach of children. Jauhkan daripada kanak-kanak.

SHELF LIFE

Observe “expired date” on outer pack.
24 months

PACKING/PACK SIZES

ERYSAA® PREFILLED SYRINGE 2,000 IU / 0.5 ml

Pack of 6 pre-filled syringes without needle-trap containing 0.5 ml solution for injection

ERYSAA® PREFILLED SYRINGE 4,000 IU / 0.4 ml

Pack of 6 pre-filled syringes without needle-trap containing 0.4 ml solution for injection

ERYSAA® PREFILLED SYRINGE 6,000 IU/0.6ml

Pack of 6 pre-filled syringes without needle-trap containing 0.6 ml solution for injection

ERYSAA® PREFILLED SYRINGE 10,000 IU/1.0ml

Pack of 6 pre-filled syringes without needle-trap containing 1.0 ml solution for injection

MANUFACTURER

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PRODUCT REGISTRATION HOLDER

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