Section 1 Name of the Medicinal Product

PANPOTIN® Pre-filled Syringe 2000IU

PANPOTIN® Pre-filled Syringe 4000IU

Section 2 Qualitative and Quantitative Composition

Trade name	Qualitative and Quantitative Composition
PANPOTIN® Pre-filled Syringe 2000IU	each pre-filled syringe (0.5 ml) contains epoietin-alfa 2,000 IU (16.8 micrograms) produced in Chinese hamster ovary by recombinant DNA technology
PANPOTIN® Pre-filled Syringe 4000IU	each pre-filled syringe (0.4 ml) contains epoietin-alfa 4,000 IU (33.6 micrograms) produced in Chinese hamster ovary by recombinant DNA technology

Section 3 Pharmaceutical Form

Solution for injection in pre-filled syringe, Colorless opalescence sterile solution in pre-filled syringe

Section 4 Clinical Particulars

4.1 Therapeutic indications

PANPOTIN is indicated for the treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adults and paediatrics aged 1 to 18 years on haemodialysis patients.

4.2 Posology and Method of Administration

Posology

All 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 epoetin alfa, and when deciding to increase the dose. In order to ensure optimum response to epoetin alfa, adequate iron stores should be assured and iron supplementation should be administered if necessary (see section 4.4).

4.2.1 Recommended dose

Treatment of symptomatic anaemia in adult chronic renal failure patients

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.

The recommended desired haemoglobin concentration range is between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L). PANPOTIN should be administered in order to increase haemoglobin to not greater than 12 g/dL (7.5 mmol/L). A rise in haemoglobin of greater than 2 g/dL (1.25 mmol/L) over a four week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.

Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin concentration range may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin concentration range of 10 g/dL (6.2 mmol/L) to 12 g/dL (7.5 mmol/L).

A sustained haemoglobin level of greater than 12 g/dL (7.5 mmol/L) should be avoided. If the haemoglobin is rising by more than 2 g/dL (1.25 mmol/L) per month, or if the sustained haemoglobin exceeds 12 g/dL (7.5 mmol/L) reduce the PANPOTIN dose by 25%. If the haemoglobin exceeds 13 g/dL (8.1 mmol/L), discontinue therapy until it falls below 12 g/dL (7.5 mmol/L) and then reinstitute PANPOTIN therapy at a dose 25% below the previous dose.

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

Caution should be exercised with escalation of ESA doses in patients with chronic renal failure. In patients with a poor haemoglobin response to ESA, alternative explanations for the poor response should be considered (see section 4.4 and 5.1).

Treatment with PANPOTIN is divided into two stages – correction and maintenance phase.

Administration by the intravenous route only

Correction phase

- The starting dose is 20-50 IU/kg, 3 times per week.
- If necessary, increase or decrease the dose by 25 IU/kg (3 times per week) until the desired haemoglobin 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 four weeks).

Maintenance phase

- The recommended total weekly dose is between 75 IU/kg and 300 IU/kg.
- Appropriate adjustment of the dose should be made in order to maintain haemoglobin values within the desired concentration range between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L).
- Patients with very low initial haemoglobin (< 6 g/dL or < 3.75 mmol/L) may require higher maintenance doses than patients whose initial anaemia is less severe (> 8 g/dL or > 5 mmol/L).

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

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.

In paediatric patients the recommended haemoglobin concentration range is between 9.5 g/dL to

11 g/dL (5.9 to 6.8 mmol/L). PANPOTIN should be administered in order to increase haemoglobin to not greater than 11 g/dL (6.8 mmol/L). A rise in haemoglobin of greater than 2 g/dL (1.25 mmol/L) over a four week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.

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

Administration by the intravenous route only

Correction phase

- The starting dose is 50 IU/kg intravenously, 3 times per week.
- If necessary, increase or decrease the dose by 25 IU/kg (3 times per week) until the desired haemoglobin 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 four weeks).

Maintenance phase

- Appropriate adjustment of the dose should be made in order to maintain haemoglobin levels within the desired concentration range between 9.5 g/dL to 11 g/dL (5.9 to 6.8 mmol/L).
- Generally, children under 30 kg require higher maintenance doses than children over 30 kg and adults. Paediatric patients with very low initial haemoglobin (< 6.8 g/dL or < 4.25 mmol/L) may require higher maintenance doses than patients whose initial haemoglobin is higher (> 6.8 g/dL or > 4.25 mmol/L)..

4.2.2 Mode of Administration

Intravenous administration (IV bolus)

- Administer over at least one to five minutes, depending on the total dose. In haemodialysed patients, a bolus injection may be given during the dialysis session through a suitable venous port in the dialysis line. Alternatively, the injection can be given at the end of the dialysis session via the fistula needle tubing, followed by 10 mL of isotonic saline to rinse the tubing and ensure satisfactory injection of the product into the circulation (see Posology, Adult haemodialysis patients).
- A slower administration is preferable in patients who react to the treatment with “flu-like” symptoms (see section 4.8).
- **Do not** administer PANPOTIN by intravenous infusion or in conjunction with other drug solutions.
- **Do not** re-use the product. After use, the rest product should be disposed. Due to the product is for single use only and does not contain a preservative.
- Please check the product by visual inspection, the product must not be colored or have some particle matters.

4.3 Contraindications

- ✘ **Do not** administer by subcutaneous injection, due to the safety and efficacy of PANPOTIN® comparison with the reference product have not been studied.
- ✘ Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- ✘ Patients who develop pure red cell aplasia (PRCA) following treatment with any erythropoietin should not receive PANPOTIN or any other erythropoietin (see section 4.4 - Pure Red Cell Aplasia).
- ✘ Uncontrolled hypertension.
- ✘ The use of PANPOTIN in patients scheduled for major elective orthopaedic surgery and not participating in an autologous blood predonation programme is contraindicated in patients with 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.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of erythropoiesis-stimulating agents (ESAs), the trade name and the batch number of the administered ESA should be clearly recorded (or stated) in the patient file.

General

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 anti-hypertensive treatment. If blood pressure cannot be controlled, epoetin alfa treatment should be discontinued.

Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have occurred also during epoetin alfa treatment in patients with previously normal or low blood pressure. Particular attention should be paid to sudden stabbing migraine-like headaches as a possible warning signal (see section 4.8).

Epoetin alfa should be used with caution in patients with epilepsy, history of seizures, or medical conditions associated with a predisposition to seizure activity such as CNS infections and brain metastases.

Epoetin alfa should be used with caution in patients with chronic liver failure. The safety of epoetin alfa has not been established in patients with hepatic dysfunction.

An increased incidence of thrombotic vascular events (TVEs) has been observed in patients receiving ESAs (see section 4.8). 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 these TVEs should be carefully weighed against the benefits to be derived from treatment with epoetin alfa particularly in patients with pre-existing risk factors for TVE, including obesity and prior history of TVEs (e.g., deep venous thrombosis, pulmonary embolism, and cerebral vascular accident).

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 concentration range for the indication of use.

There may be a moderate dose-dependent rise in the platelet count within the normal range during treatment with epoetin alfa. 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.

All 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 epoetin alfa, 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 epoetin alfa, adequate iron stores should be assured and iron supplementation should be administered if necessary (see section 4.2):

- For chronic renal failure patients, iron supplementation (elemental iron 200 to 300 mg/day orally for adults and 100 to 200 mg/day orally for paediatrics) is recommended if serum ferritin levels are below 100 ng/mL.

Very rarely, development of or exacerbation of porphyria has been observed in epoetin alfa-treated patients. Epoetin alfa should be used with caution in patients with porphyria.

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. More severe cases have been observed with long-acting epoetins.

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, PANPOTIN

should be withdrawn immediately and an alternative treatment considered.

If the patient has developed a severe cutaneous skin reaction such as SJS or TEN due to the use of PANPOTIN, treatment with PANPOTIN must not be restarted in this patient at any time.

Patients should not be switched from one ESA to another.

Pure Red Cell Aplasia

Antibody-mediated pure red cell aplasia (PRCA) has been reported after months to years of epoetin alfa treatment.

Cases have also been reported in patients with hepatitis C treated with interferon and ribavirin, when ESAs are used concomitantly. Epoetin alfa is not approved in the management of anaemia associated with hepatitis C.

In patients developing sudden lack of efficacy defined by a decrease in haemoglobin (1 to 2 g/dL per month) with increased need for transfusions, a reticulocyte count should be obtained and typical causes of non-response (e.g. iron, folate or Vitamin B12 deficiency, aluminium intoxication, infection or inflammation, blood loss, haemolysis and bone marrow fibrosis of any origin) should be investigated.

A paradoxical decrease in haemoglobin and development of severe anaemia associated with low reticulocyte counts should prompt to discontinue treatment with epoetin alfa and perform anti-erythropoietin antibody 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.

Treatment of symptomatic anaemia in adult and paediatric 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 (0.62 mmol/L) per month and should not exceed 2 g/dL (1.25 mmol/L) 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 haemoglobin concentration range as recommended in section 4.2. In clinical trials, an increased risk of death and serious cardiovascular events was observed when ESAs were administered to achieve a haemoglobin concentration level of greater than 12 g/dL (7.5 mmol/L).

Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when haemoglobin concentration is increased beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.

Caution should be exercised with escalation of PANPOTIN doses in patients with chronic renal failure since high cumulative epoetin doses may be associated with an increased risk of mortality, serious cardiovascular and cerebrovascular events. In patients with a poor haemoglobin response to epoetins, alternative explanations for the poor response should be considered (see section 4.2 and 5.1).

Some patients with more extended dosing intervals (greater than once weekly) of epoetin alfa may not maintain adequate haemoglobin levels (see section 5.1) and may require an increase in epoetin alfa dose. Haemoglobin levels should be monitored regularly.

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 though causality has not been established. Serum electrolytes should be monitored in chronic renal failure patients. If an elevated or rising serum potassium level is detected, then in addition to appropriate treatment of the hyperkalaemia, consideration should be given to ceasing epoetin alfa administration until the serum potassium level has been corrected.

An increase in heparin dose during haemodialysis is frequently required during the course of therapy with epoetin alfa as a result of the increased packed cell volume. Occlusion of the dialysis system is possible if heparinisation is not optimum.

Excipients

This medicinal product contains Sodium Phosphate monobasic dihydrate, Sodium Phosphate dibasic dihydrate and Sodium chloride, should use with caution in patients who need to restrict sodium salt intake.

4.5 Interaction with other medicinal products and other forms of interaction

No evidence exists that indicates that treatment with epoetin alfa alters the metabolism of other drugs. Drugs that decrease erythropoiesis may decrease the response to epoetin alfa.

Since cyclosporin is bound by RBCs there is potential for a drug interaction. If epoetin alfa is given concomitantly with cyclosporin, blood levels of cyclosporin should be monitored and the dose of cyclosporin adjusted as the haematocrit rises.

No evidence exists that indicates an interaction between epoetin alfa and G-CSF or GM-CSF with regard to haematological differentiation or proliferation of tumour biopsy specimens in vitro.

In female adult patients with metastatic breast cancer, subcutaneous co-administration of 40,000

IU/mL epoetin alfa with trastuzumab 6 mg/kg had no effect on the pharmacokinetics of trastuzumab.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Studies in animals have shown reproduction toxicity (see section 5.3). Consequently, epoetin alfa should be used in pregnancy only if the potential benefit outweighs the potential risk to the foetus.

Breastfeeding

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

Fertility

There are no studies assessing the potential effect of epoetin alfa on male or female fertility.

4.7 Effects on ability to drive and use machine

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

4.8 Undesirable effects

To determine long term safety, the TEAEs that had occurred in 274 subjects administered at least one dose of PANPOTIN® 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 reference product group during the maintenance phase was also presented as a reference (Lim, 2021)

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 PANPOTIN® and Reference Product. Among 274 subjects in the PANPOTIN® group who had received at least one dose of PANPOTIN® 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 PANPOTIN® 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)

	PANPOTIN® **% (N=274)**	**Reference (N=146)**
Subjects with TEAEs	61.68	60.27
Infections and infestations		
- 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
- Diarrhea	4.38	2.74
- Constipation	1.46	2.74
- Gastritis	2.19	0
- Abdominal pain	0.73	2.05
- Upper gastrointestinal hemorrhage	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

	PANPOTIN® % (N=274)	Reference (N=146)
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 version: 19.0.

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

By SOC, the most common ADR in the PANPOTIN® 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', 'Hemorrhage 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

	PANPOTIN® % (N=274)	Reference (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
- Hemorrhage 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.

4.9 Overdose

The therapeutic margin of epoetin alfa is very wide. Overdosage 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.

Section 5 Pharmacological Properties

5.1 Pharmacodynamic Properties

Therapeutic group: BLOOD AND BLOOD FORMING ORGANS; ANTIANEMIC PREPARATIONS; OTHER ANTIANEMIC PREPARATIONS; Other antianemic preparations; erythropoietin (ATC code: B03XA01)

5.1.1 Mechanism of action

Erythropoietin (EPO) is a glycoprotein hormone produced primarily by the kidney in response to hypoxia and is the key regulator of red blood cell (RBC) production. EPO is involved in all phases of erythroid development, and has its principal effect at the level of erythroid precursors. After EPO binds to its cell surface receptor, it activates signal transduction pathways that interfere with apoptosis and stimulates erythroid cell proliferation. Recombinant human EPO (epoetin alfa), expressed in Chinese hamster ovary cells, has a 165 amino acid sequence identical to that of human urinary EPO; the 2 are indistinguishable on the basis of functional assays. The apparent molecular weight of erythropoietin is 32,000 to 40,000 dalton.

Erythropoietin is a growth factor that primarily stimulates red cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells.

5.1.2 Pharmacodynamic effects

Healthy volunteers

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

Phase I study (PG-EPO-Ph1) in healthy subjects provided comparative pharmacodynamic data on PANPOTIN® versus Reference Product. For 27 subjects who completed the study per protocol, the blood levels of RBC, hemoglobin, hematocrit and reticulocyte were determined up to 28 days following single-dose intravenous administration of Reference Product or PANPOTIN® 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 Reference Product and PANPOTIN®. E_{max} was 95.4(±21.7)*10^3/μL and 93.4(±24.2) *10^3/μL for Reference Product and PANPOTIN®, respectively and $AUEC_{last}$ was 1773.6(±404.0) *10^3/μL*day and 1832.6(±414.4) *10^3/μL*day for Reference Product and PANPOTIN®, 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 PANPOTIN® and Reference Product.

5.1.3 Mechanism of toxication

Not Available

5.1.4 Immunogenicity

The result form the study in 132 subjects were treated with PANPOTIN® for 52 weeks (=12 months). 117 subjects were treated with PANPOTIN® for 24 weeks after conversion from the reference product to PANPOTIN® (Lim, 2021).

Blood samples for the assessment of immunogenicity were collected at the baseline, at week 28 and at week 52 and all samples from the subjects were determined as a negative. Results of anti-epoetin testing at these time points demonstrated that there was no incidence of anti-epoetin Ab in the PANPOTIN® arm and reference product arm during 28 weeks treatment period at maintenance phase. And there was no anti-epoetin Ab cases in the 132 subjects who treated with PANPOTIN® for a total of 52 weeks and 117 subjects who switched from the reference product to PANPOTIN® and treated with PANPOTIN® for 24 weeks.

5.2 Pharmacokinetic Properties

Healthy volunteers

After single I.V. bolus (100 IU/kg) of PANPOTIN® 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 PANPOTIN® in comparison to Reference Product. 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 Reference Product or PANPOTIN® 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 Reference Product and PANPOTIN® treatment groups. C_{max} was 2518.50(±269.30) mIU/mL and 2531.21(±272.50) mIU/mL for Reference Product and PANPOTIN®, respectively, and AUC_{last} was 17094.51(±2141.31) hr*mIU/mL, and 16464.51(±1872.40) hr*mIU/mL for Reference Product and PANPOTIN®, respectively. In addition, respective CL values for Reference Product and PANPOTIN® 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 PANPOTIN® and Reference Product.

5.3 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 PANPOTIN® and comparator drug Reference Product. 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.

Section 6 Pharmaceutical Particulars

6.1 List of excipients

Sodium Phosphate monobasic dihydrate, Sodium Phosphate dibasic dihydrate, Glycine, Polysorbate 80, Sodium chloride, and Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

24 months

6.4 Special precautions for storage

- Store at (2℃ ~ 8℃).
- ❖ **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.
- Keep out of reach of children

6.5 Nature and contents of container

PANPOTIN® is filled in a pre-filled syringe (type I glass barrel) closed with plunger stopper (FluroTec-coated bromobutyl rubber) and needle size 27G x ½" with a needle cover – packed in a carton as below.

PANPOTIN® per pre-filled syringe	Volume	Carton pack size
Epoetin-alfa 2,000IU (16.8 µg)	0.5 mL	6 pre-filled syringes/box
Epoetin-alfa 4,000IU (33.6 µg)	0.4 mL	6 pre-filled syringes/box

Section 7 Marketing Authorization Holder

7.1 Marketing Authorization Holder

S. Charoen Bhaesaj Trading Co., Ltd.
711,713-715-717 Mahachai Road, Wangburapapirom,
Pranakorn, Bangkok, THAILAND, 10200
Tel: (+66) 2621 1301, Fax: (+66) 2621 1310

7.2 Manufacturers

Finished Product and Batch Certification Manufacturer

PanGen Biotech Inc.
4F Innoplex 2-dong 306, Sinwon-ro, Yeongtong-gu, Suwon-si, Gyeonngi-do,
Republic of Korea (South Korea)

Primary and Secondary Packing Manufacturer

Korea Vaccine Co., Ltd.
128, Mongnae-ro, Danwon-gu, Ansan-si, Gyeonggi-do, Republic of Korea (South Korea)

Section 8 Marketing Authorization Numbers

Reg No.	Name of Biosimilar Product	Reference Product
1A XXX/XX (NBS)	PANPOTIN® Pre-filled Syringe 2000IU	*Eprex (PREFILLED SYRINGE 2,000 IU/0.5 ML)*
1A XXX/XX (NBS)	PANPOTIN® Pre-filled Syringe 4000IU	*Eprex (PREFILLED SYRINGE 10,000 IU/1 ML)*

Section 9 Date of First Authorization/Renewal of the Authorization

MM DDDD YYYY

Section 10 Date of revision of the text

Updated on 05/06/67

Reference

Lim, S. K. (2021). A multicentre, multi-national, double-blind, randomised, active-controlled, parallel-group clinical study to assess the safety and efficacy of PDA10 (Epoetin-Alfa) vs. Eprex® in patients with anaemia of chronic renal failure. *22*(1).