SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
EPOSINO

2. Qualitative and quantitative composition
A pre-filled syringe of 1 mL contains 2,000 IU or 4,000 IU of human erythropoietin.
Each 1ml contains:

Active Ingredients:	Quantity
Human erythropoietin	2000IU 4000IU
Non-active ingredient(s):	
Human Serum Albumin	2.500mg
Sodium Citrate Dihydrate	5.882mg
Citric Acid Monohydrate	0.063mg
Sodium Chloride	5.844mg
Water for injection	Add to 1ml

3. Pharmaceutical form
Solution for injection in pre-filled syringe.
Clear, colorless liquid.

4. Clinical particulars
4.1 Therapeutic indications
1) Anemia resulting from renal function insufficiency, including hemodialysis and non-hemodialysis
2) Red blood cell mobilization during surgical perioperative period.

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 human erythropoietin, 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.

Treatment of Renal anemia

This product should be administered through subcutaneous and intravenous way 2-3 times per week under physicians' direction. Dosage can be changed according to anemia status, age, and other related factors of patients.

Treatment period: The initial dosage for the patients receiving hemodialysis is 100-150 IU/kg, and for those not on hemodialysis is 75-100 IU/kg per week. If hematocrit increase is not as expected (<0.5vol/week), the dosage can be changed after 4 weeks of initial treatment to increase the dose at 15-30 IU/kg per week, but not more than 30 IU/kg per week. The expected rise of hematocrit should be up to 30-33vol%, not higher than 36vol%.

Maintenance period: If the hematocrit has reached 30-33vol/% and/or the hemoglobin has reached 100-110g/l, the maintenance treatment period starts. The dosage should be 2/3 of the initial dosage on this stage. The hematocrit should be monitored once every 2-4 weeks so as to adjust the dosage to maintain hematocrit and hemoglobin at the proper level as well as to avoid erythropoesis to be formed too quickly.

Treatment of Red blood cell mobilization during surgical perioperative period.

Suitable for use by elective surgical patients with preoperative hemoglobin value in the 100-130 g / L of (except for cardiovascular surgery patients), using a dose 150IU/ kg of body weight subcutaneously, three times a week, from 10 days prior to surgery patients to 4 days after application. It can relieve anemia during and after surgery and reduce the demand for allogeneic blood transfusion, speed up the recovery of postoperative anemia tend. In order to prevent iron deficiency during the drug use period, iron should be supplemented at the same time.

4.3 Contraindications

Patients with uncontrollable severe hypertension

Those allergic to this product or to other erythropoietin agents, those allergic to human serum albumin.

Those with combined infections, which should be cured before the product is administered.

4.4 Special warnings and precautions for use

Take special care with EPOSINO

1) According to literature report, in clinical studies on chronic renal failure patients, after administration of erythropoietin drugs (ESAs), when the hemoglobin level ≥13g/dL, the patient death, serious cardiovascular events and stroke risk increase, use personalized administration regimen to achieve and maintain hemoglobin levels within the 10g/dL-12g/dl.

In clinical studies, when chronic renal failure patients with hemoglobin level ≥ 13g/dL were given ESAs treatment, the death, serious cardiovascular events and stroke risk is higher. For chronic renal failure patients with inadequate response to ESA treatment, the risk of cardiovascular events and death is higher than other patients. In controlled clinical studies on cancer patients, ESAs can increase the mortality and the risk of serious cardiovascular events. These events include myocardial infarction, stroke, congestive heart failure, Hemodialysis and vascular access thrombosis. These risks may be produced due to the level of hemoglobin rising by more than lg/dl within two weeks.

2) According to report in the literature, in clinical studies on breast cancer, non-small cell lung cancer, head and neck cancer, lymphoma and cervical cancer patients, ESAs may shorten the patient's survival and / or increase the risk of tumor progression or recurrence. To reduce those risks including serious cardiovascular thrombotic events, minimum dose should be used to avoid the red blood cell transfusion. ESAs can only be used for anemia induced by chemotherapy of bone marrow suppression. ESAs do not apply to bone marrow suppression treatment in patients whose anemia symptoms disappeared. After chemotherapy treatment, you should stop using ESAs.

3) According to report in the literature, use of human erythropoietin in patients without receiving preventive anticoagulant treatment during perioperative period can increase the occurrence of deep vein thrombosis.Attention should be payed to the prevention of deep vein thrombosis.

4) As reported in the literature, for patients with pure red cell aplasia (PRCA) and severe anemia accompanied with or without other cytopenias, erythropoietin neutralizing antibodies appeared. The above report is mainly seen in CRF (chronic renal failure) patients receiving subcutaneous ESAs treatment. According to another report, PRCA is also found in patients given ESAs during treatment of hepatitis C with interferon and ribavirin. If a patient suddenly loses response to the product accompanied by severe anemia and decreased reticulocyte count, the reasons for failure of this product should be immediately assessed, including appearance of erythropoietin neutralizing antibodies. If it’s suspected to be erythropoietin antibody-related anemia, you should disable use of ESAs. For antibody-mediated anemia, use of human erythropoietin should be permanently discontinued. Because of possible cross-reaction of antibodies, it cannot be changed to other ESAs drugs.

Take general care with EPOSINO

1) In the parenteral administration of biological products, pay attention to allergies or other adverse events:

2) During the treatment with “EPOSINO”, the hematocrit should be checked regularly (once a week at the early stage and once every two weeks in the maintenance period). The hematocrit should be maintained under 36vol/% to avoid the formation of extraordinary erythropoiesis. If excessive red blood cell growth is found, suitable treatment shall be taken such as stopping the use of EPOSINO temporarily. When using

36000IU /syringe, check the hemoglobin regularly (once every one to two weeks). When the hemoglobin is higher than 120g/L, the administration is not recommended to continue. In case of excessive red blood cell growth, take appropriate measures.

3) In CRF patients receiving treatment, it's rarely seen to have worse hemoporphyrin. Hematoporphyrin patients should use human erythropoietin with caution. During treatment, absolute or functional iron deficiency may occur. In functional iron deficiency, the ferritin levels is normal, but transferrin saturation can decrease, the reason may be that stored iron in the body cannot be quickly mobilized and released to meet the increased demand for iron under the effect of erythropoietin to stimulate the bone marrow hemopoiesis. Transferrin saturation should be ≥ 20%, ferritin should be ≥ l00ng/ml. Before and during treatment with the drug, patients should receive iron status assessment, indicators include: transferrin saturation (mean ratio of serum iron and transferrin bondability) and serum ferritin. In fact, all patients eventually need to supplement iron to increase or maintain transferrin saturation to meet the need of erythropoiesis promoted by the product. Surgery patients using this product should be supplemented with iron throughout the course of treatment to support erythropoiesis and avoid depletion of iron stores.

4) This product can cause increased blood pressure during treatment, so the blood pressure should be adequately controlled before treatment. In early treatment, when the hematocrit increases, about 25% of dialysis patients need to start or strengthen anti-hypertensive treatment. During treatment with the drug, blood pressure of patients should be strictly monitored and controlled. Patients should be informed of antihypertensive treatment and the importance of dietary restrictions. If blood pressure is difficult to control, reducing or stop using this product can reduce the hemoglobin.

If at any time within two weeks, hemoglobin increases by more than lg/dL, it's recommended to reduce the product's dose, because aggravation of high blood pressure may be related to the rapid growth of hemoglobin. For patients with CRF receiving hemodialysis treatment have clinically significant ischemic heart disease or congestive heart failure, the dosage of the product should be carefully adjusted to achieve and maintain hemoglobin levels between the 10-12g/dL.

5) For patients with a history of seizures or blood disease (such as sickle-cell anemia disease, myelodysplastic syndrome or high-blood clotting disorder), the drug safety and effectiveness remain unclear.

In view of the increased risk of epilepsy during first 90 days of treatment, blood pressure and neurological aura symptoms should be closely monitored. In the meantime, patients should avoid engaging in potentially hazardous activities such as driving or operating heavy machinery.

6) During hemodialysis, the patients taking the drug needs to be strengthened with heparin anticoagulation treatment to prevent artificial thrombus coagulation of kidney. In treatment of adult patients with CRF associated with ischemic heart disease or of congestive heart failure, compared with standard hematocrit of 30%, patients with

standard hematocrit of 42% (normal hematocrit) have higher risks of thrombus events (including vascular access thrombosis). Patients previously with cardiovascular disease should be closely monitored.
7) The drug should be used carefully for the patients with myocardial infarction or pulmonary infarction, cerebral infarction or those with allergic history or tendency.
8) Folic and VitaminB12 insufficiency and ultra-high aluminum may reduce efficacy of EPOSINO.
9) Hyperkalemia may slightly rise during the course of treatment, diet should be adjusted or the dosage should be adjusted according to doctor's advice when hyperkalemia occurs until the normal level is recovered.
10) Pre-filled syringes with cracks, breakage, turbidity, precipitation and other phenomena cannot be used. This product should be used up at one time after being opened and cannot be used again.
11) Athletes should use it with caution.

Aged patients
For aged patients when EPOSINO is used, the blood pressure and hemotocrit should be monitored frequently, and the dosage and times of administration should be adjusted accordingly.

Patients scheduled for major elective orthopaedic surgery
In patients scheduled for major elective orthopaedic surgery, EPOSINO has been shown to hasten erythroid recovery (increased haemoglobin levels, haematocrit levels, and reticulocyte counts). While on EPOSINO, some people need medicines to reduce the risk of blood clots. If you can't take medicines that prevent blood clotting, you must not have EPOSINO.

4.5 Interaction with other medicinal products and other forms of interaction
No evidence exists that indicates that treatment with opoetin alfa alters the metabolism of other drugs.
Drugs that decrease erythropoiesis may decrease the response to human erythropoietin.
Iron supplements and other blood stimulants may increase the effectiveness of human erythropoietin.
Since cyclosporin is bound by RBCs there is potential for a drug interaction. If human erythropoietin is given concomitantly with cyclosporine, blood levels of cyclosporine should be monitored and the dose of cyclosporine adjusted as the haematocrit rises.

4.6 Fertility, pregnancy and lactation
<u>Pregnancy</u>

There are no adequate and well-controlled studies in pregnant women. Studies in animals have shown reproduction toxicity. Consequently, human erythropoietin should be used in pregnancy only if the potential benefit outweighs the potential risk to the foetus.

Breastfeeding

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

The use of human erythropoietin is not recommended in lactating surgical patients participating in an autologous blood predonation programme.

Fertility

There are no studies assessing the potential effect of human erythropoietin on male or female
fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

1) Common reactions: A few may have headache, low fever and fatigue and only few may have muscle pain and arthralgia at the initial stage of drug administration. But most of the side reactions may be relieved through the treatment and no need to discontinue the use of the drug. If the above –mentioned symptoms still exist, stopping using the drug may be considered.

2) Allergic reactions: Allergic reactions such as skin rashes or urticaria, including allergic shock may occur rarely, therefore, it is advised that a small dosage of the drug should be used as an initial dose as well as in the beginning of reuse of the drug, make sure no abnormal reactions occurs before the use of full dose as prescribed. If it does occur, the drug should be stopped immediately and the proper treatment provided.

3) Cardiovascular System: Hypertension or other symptoms caused by the exacerbation of existing hypertension and hypertensive encephalopathy may occur such as headache, disturbance of consciousness, convulsion and sometimes even encephalorrhagia. Therefore, blood pressure should be monitored periodically, the drug dosage may be decreased or stopped, and the depressor drug may also be adjusted.

4) Hematological System: The blood viscosity may increase obviously as hematocrit rises. It should be noted to prevent the forming of thrombus.

5) Liver: Hepatic function impairment may occur, GOP and GPT sometimes may rise up.
6) Gastrointestinal System: Nausea, vomiting, anorexia and diarrhea may happen occasionally when the drug is used.

4.9 Overdose
It may increase hematocrit too much and cause fatal complications of cardiovascular system.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: anti-anaemic, ATC code: B03XA01.

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. Erythropoietin, 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.

Pharmacodynamic effects

5.2 Pharmacokinetic properties
Drug injected subcutaneously is absorbed slowly, concentration of erythropoietin in serum rises 2 hours later, it takes 18 hours for the drug concentration in blood to reach the peak value, bone marrow is special takein organ, the drug is mainly taken by liver and kidney, the drug is mostly metabolized in the body after administration, animal (rat) test shows that a small amount of EPO was also degraded in kidney, bone marrow and spleen, in addition to liver, Kidney was not the main organ for eliminating EPO, anemia patients using EPO excrete less than 10% of the drug in original form through the kidney.

5.3 Preclinical safety data
Toxicology:

1) Acute toxicity: LD_{50} of injection in intravenous injection into mouse, rat, dog and 4 –day old immature rat is more than 20000IU/kg.
2) Subacute toxicity and chronic toxicity
Rat: Subacute toxicity and chronic toxicity test on female and male rat receiving intravenous or intraperitoneal injection in the 4th week, 13th week and 52nd week shows that plethora is caused due to excessive pharmacological action after administration of the drug in the 4th week, 13th week and 52nd week at the dosage of 80IU/kg/day, 20IU/kg/day and 10IU/kg/day respectively, and long-term administration of the drug can result in fibrosis of marrow.
Dog: Subacute toxicity and chronic toxicity test on female and male dog receiving intravenous or intraperitoneal injection in the 4th week, 13th week and 52nd week shows that plethora is caused due to excessive pharmacological action after administration of the drug in the 4th week, 13th week and 52nd week at the dosage of 200IU/kg/day, 100IU/kg/day and 20IU/kg/day respectively, and long-term administration of the drug can result in fibrosis of marrow and change of kidney structure.

6. Pharmaceutical particulars

6.1 List of excipients
Human serum albumin, Sodium citrate dihydrate, Citric acid monohydrate, 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
32 months.

6.4 Special precautions for storage
Store at 2-8 degree Celsius, protect from light and do not freeze and shake.

6.5 Nature and contents of container
2000IU or 4000IU per ml in pre-filled syringe, one syringe is packed in a small box, and 10 small boxes are packed in a middle box.

6.6 Special precautions for disposal and other handling
The product should not be used, and discarded
- if the seal is broken,
- if the liquid is coloured or you can see particles floating in it,
- if you know, or think that it may have been accidentally frozen, or
- if there has been a refrigerator failure.

The product is for single use only. Only take one dose of EPOSINO from each syringe. In case only a partial dose of the syringe is required, the cover should be removed before the plunger is pushed up to the desired numbered graduation
mark to remove unwanted solution before injection. Refer to section 3. How to use EPOSINO (instructions on how to inject EPOSINO) of the package leaflet.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Manufacturer

Kexing Biopharm Co., Ltd.
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