Eposis
Erythropoietin

COMPOSITION
Eposis Injection: Each pre-filled syringe contains 0.5 ml solution containing Erythropoietin Concentrated Solution BP 2000 IU.
Eposis 3000 Injection: Each pre-filled syringe contains 0.75 ml solution containing Erythropoietin Concentrated Solution BP 3000 IU.
Eposis 4000 Injection: Each pre-filled syringe contains 0.4 ml solution containing Erythropoietin Concentrated Solution BP 4000 IU.
Eposis 5000 Injection: Each pre-filled syringe contains 0.5 ml solution containing Erythropoietin Concentrated Solution BP 5000 IU.
Eposis 10000 Injection: Each pre-filled syringe contains 1.0 ml solution containing Erythropoietin Concentrated Solution BP 10000 IU.

PHARMACOLOGICAL ACTION
Erythropoietin is an endogenous glycoprotein that stimulates red blood cell production. Erythropoietin alfa (rch) is purified from a Chinese hamster ovary cell line into which the gene coding for human erythropoietin has been inserted. The molecular weight is about 30,400 daltons and the protein moiety, a single chain polypeptide of 165 amino acids, has a molecular weight of 18,244 daltons. The carbohydrate moiety with three N-linked and one 0-linked carbohydrate groups corresponds to a weight fraction of approximately 40%. Erythropoietin alfa (rch) is indistinguishable from human erythropoietin in biological activity and immunological reactivity.

CLINICAL PHARMACOLOGY
The molecular weight of EPOSIS is approximately 30,000 daltons. Sixty percent of the molecular weight is contributed by the protein fraction; this is made up of 165 amino acids. The compound has four carbohydrate chains. These four carbohydrate chains are attached to the protein with three N-glycosidic bonds and one O-glycosidic bond. Genetic engineering technology is employed to obtain this product which has the same amino acid sequence as erythropoietin obtained from the urine. The gene coding for erythropoietin has been inserted into mammalian cells to develop recombinant EPOSIS producer cell strain. The recombinant producer cells strain is employed to produce the secretory product which is purified to homogeneity.

PHARMACOKINETIC PROPERTIES
S.C. Route: The serum concentrations of erythropoietin obtained with subcutaneous injection are lower than with intravenous injection. The levels of the compound increase slowly in the serum, and peak levels are reached 12 to 18 hours after the dose. The half-life following subcutaneous injection is about 24 hours.

IV Route: The volume of distribution is similar to the plasma volume. When given by the intravenous route, the half-life is 5-6 hours, independent of the disease state.

THERAPEUTIC INDICATIONS
-Treatment of anaemia due to erythropoietin deficiency in adult chronic renal failure patients and in predialysis, haemodialysis, peritoneal dialysis patients and in paediatric patients on haemodialysis. -Treatment of anaemia in cancer patients with non-myeloid malignancies (with or without chemotherapy) and prevention of anaemia in cancer patients with non-myeloid malignancies who are undergoing chemotherapy treatment. -Treatment of anaemia in HIV-infected patients on zidovudine with endogenous erythropoietin levels <500 mU/mL. -To aid autologous blood collection in patients scheduled for elective surgery, with haematocrits of 33-39%, who cannot produce the required blood without exogenous erythropoietin, - EPOSIS is indicated in adult patients scheduled for elective surgery with mild to moderate anaemia (haemoglobin 10 to 13 g/dL) in whom moderate blood loss of 2-4 units is expected.

DOSAGE & ADMINISTRATION
Table for General Guidelines
Target haemoglobin concentration 11-12 g/dl (adults), 9.5-11 g/dl (children) Target haematocrit is 33 - 36%

Indication	Initial dose	Maintenance dose
Chronic renal failure	50 -100 IU/ kg 3 times/week, IV/SC	Decrease the dose by 25 IU/ kg/dose to maintain target haemoglobin
Adult predialysis patients	50-100 IU/ kg 3 times/week, IV/SC	17-33 IU/ kg 3 times/week
Adult haemodialysis patients	50-100 IU/ kg 3 times/week, IV/SC	30-100 IU/ kg 3 times/week
Adult peritoneal dialysis patients	50 IU/ kg 2 times/week, SC	25-50 IU/ kg 2 times/week
Paediatric haemodialysis patients	50 IU/ kg 3 times/week, IV	Dose IU/ kg 3 times/week Weight (kg) Maintenance <10 75-150 10-30 60-150 >30 30-100
Cancer patients	150 IU/ kg 3 times/week, SC	If Hb concentration increases/month (1) < 1g /dl - double the dose (2) > 2 g / dl - reduce dose by 25%
HIV infected patients on zidovudine	100 IU/ kg 3 times/week for 8 weeks SC/ IV	
Adult surgery patients in an autologous pre donation program	600 IU/ kg 2 times/week IV, for 3 weeks prior to surgery	
Perisurgery patients without autologous blood donation	600 IU/ kg once a week SC for 3 weeks prior to surgery or 300 IU/kg daily for 10 days before surgery & repeat on day of surgery, continue for 4 days after surgery	

Chronic Renal Failure Patients
IV EPOSIS may be administered by subcutaneous or intravenous route. When changing the route of administration, the same dose should be used initially and then adjusted to keep haemoglobin in the target range. EPOSIS is administered so as to maintain haemoglobin concentration between 11 to 12 g/dl or haematocrit of 33-36% in adults and 9.5 to 11 g/dl in children. The starting dose is usually 50 to 100 IU/kg thrice a week by IV or SC route.

During the correction phase, the EPOSIS dose should be increased if the haemoglobin does not increase at least 1 g/dl/month or an increase in haematocrit of less than 2% over 2 - 4 week period does not take place. An increase in haemoglobin concentration is usually observed between 2 and 10 weeks. Once the required haemoglobin concentration is achieved, the dose is decreased by 25 IU/kg/dose so that the haemoglobin concentration remains in the required range. Whenever the haemoglobin concentration exceeds 12 g/dl, therapy is stopped. Dose reduction is made either by omitting one of the weekly doses or by reducing the amount per dose.

Adult Predialysis Patients
Initial Dose: 50 IU/kg thrice a week by subcutaneous or intravenous route. Dosage adjustments of 25 IU/kg/dose are made at intervals of at least 4 weeks until the required haemoglobin concentration is attained.

Maintenance Dose: The usual maintenance dose is 17 to 33 IU/kg thrice a week.

Adult Haemodialysis Patients
Initial Dose: 50 IU/kg is given thrice a week by subcutaneous or intravenous route. Dose adjustments are made in increments of 25 IU/kg per dose at intervals of 4 weeks until the required haemoglobin concentration is achieved.

Maintenance Dose: The usual dose to maintain the haemoglobin concentration is between 30 and 100 IU/kg thrice a week.

In patients who have severe anaemia (haemoglobin < 6 g/dl) the maintenance dose required is usually higher.

Adult Peritoneal Dialysis patients
Initial Dose: 50 IU/kg twice a week by subcutaneous route. Dose adjustments are made in the dose of 25 IU/kg twice a week every 4 weeks until the required haemoglobin concentration is achieved.

Maintenance Dose: The usual dose is 25 and 50 IU/kg twice a week.

Paediatric Haemodialysis Patients
Correction Dose: 50 IU/kg thrice a week by the intravenous route. Dosage adjustments of 25 IU/kg/dose are made at intervals of 4 weeks until haemoglobin concentration is achieved. haemoglobin increase continues to be < 1 g/dL, response is unlikely and treatment should be discontinued. If following therapy, the haemoglobin increases by more than 2 g/dl per month or haematocrit rises by > 4 points over a two week period, the EPOSIS dose should be reduced by 25%. If the haemoglobin exceeds 14 g/dl, therapy is discontinued until it falls below 12 g/dL and then EPOSIS is resumed at a dose 25% lower than the previous dose. The need for EPOSIS therapy should be re-evaluated after completion of chemotherapy.

HIV-infected Patients on Zidovudine Treatment
The serum erythropoietin level is determined prior to transfusion. Patients with serum erythropoietin levels > 500 mil/ml are unlikely to respond to EPOSIS therapy.

Initial Dose: 100 IU/kg thrice a week for 8 weeks by subcutaneous or intravenous route. If the response is unsatisfactory after 8 weeks of therapy, the dose of EPOSIS is increased. Dose increases are made at intervals of 4 weeks in increments of 50-100 IU/kg thrice a week. If patients do not respond satisfactorily to a dose of 300 IU/kg thrice a week, response at higher doses is unlikely.

Maintenance Dose: The dose is titrated to maintain the haematocrit between 33-36%. If the haematocrit exceeds 40%, the dose is withheld until the haematocrit falls to 36%. At resumption of treatment, dose is reduced to 25% of the original dose.

Adult Surgery Patients in an Autologous Pre-Donation Program
In patients with deficiency, 200 mg of oral elemental iron should be prescribed per day; the supplementation should continue throughout the course of therapy. Usually patients are given 600 IU/kg of IV twice a week. In some patients, a dose of 150-300 IU/kg of EPOSIS given twice a week is found to be sufficient. EPOSIS is generally given for three weeks prior to surgery. At each visit, one unit of blood is collected for autologous transfusion while maintaining the patients' haematocrit at 33% and haemoglobin >11g/dL.

Perisurgery patients (without autologous blood donation)
in patients with deficiency, 200 mg of oral elemental iron should be prescribed per day; the supplementation should continue throughout the course of therapy. In patients conforming to the requirements for autologous blood donation, 600 IU/7 kg of EPOSIS is given once a week via the subcutaneous route for three weeks prior to surgery. The dose is repeated on the day of surgery. When it is necessary to expedite the process before surgery to less than three weeks, 300 IU/kg of EPOSIS is given daily for 10 days. The dose is repeated on the day of surgery and for four days after surgery.

USE IN PREGNANCY & LACTATION
EPOSIS should be used during pregnancy, only if the potential benefit justifies the potential risk to the fetus. It is not known whether EPOSIS is excreted into human milk and therefore it should be used with caution in nursing women.

SIDE EFFECTS
Hypertension is the most frequently occurring adverse reaction. Vascular events such as cerebrovascular accidents, transient ischemic attacks, aneurysms, deep venous thrombosis, myocardial infarction, pulmonary emboli and clotting of an artificial kidney, Skin rashes, eczema, urticaria skin reactions at the injection site, increased blood potassium, phosphate levels, increased blood urea nitrogen, creatinine, and increased uric acid have been reported.

CONTRAINDICATIONS
Uncontrolled hypertension, Hypersensitivity to any of the components of this product, patients with severe coronary, peripheral arterial, carotid or cerebral vascular disease.

PRECAUTION
People with severe anaemia usually feel very tired and sick. When EPOSIS begins to work, usually in about 6 weeks, most people start to feel better. Some people are able to be more active. However, EPOSIS only corrects anaemia. It has no effect on kidney disease or any other medical problem that needs regular medical attention. Therefore, even if you are feeling much better, it is very important that you do not miss any appointments with your doctor or any dialysis treatments.

Many people with kidney problems need to be on a special diet. Also, people with high blood pressure (which may be caused by kidney disease or by EPOSIS treatment) may need to be on a special diet and/or to take medicine to keep their blood pressure under control. After their anaemia has been corrected, some people feel so much better that they want to eat more than before. To keep your kidney disease or your high blood pressure from getting worse, it is very important that you follow your special diet and take your medicines regularly, even if you are feeling better.

In addition to EPOSIS, your body needs iron to make red blood cells. Your doctor may direct you to take iron supplements. He or she may also direct you to take certain vitamins that help the iron work better. Be sure to follow your doctor's orders carefully. Because EPOSIS will not work properly if there is not enough iron in your body.

SPECIAL PRECAUTIONS FOR STORAGE
Store between 2°C and 8°C, do not shake or freeze and do not expose to light.

OVER DOSAGE
EPOSIS has a very wide safety margin. In cases of over dosage, the pharmacological effects of the hormone are pronounced. When extremely high haemoglobin levels occur, phlebotomy may provide the solution. Supportive care is provided depending on the symptoms of over dosage.

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

PHARMACEUTICAL INFORMATION
Storage Conditions
Store in original carton at 2°C to 8°C. Do not freeze or shake. Protect from light. Keep out of the reach of children.

Presentation & Packaging
Eposis Injection: Each commercial box contains one pre-filled syringe containing Erythropoietin Concentrated Solution BP 2000 IU and one alcohol pad.
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Manufactured By
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