EPOETIN ALFA

WEPOX® 4000

4,000 IU/mL Solution for Injection

(IV/ SC)

Antianemic Preparations

FORMULATION
Each 1.0 mL prefilled syringe contains:
Recombinant Human Erythropoietin ... 4000IU
Derived from Chinese Hamster Ovary (CHO) cells by recombinant DNA technology with HSA as stabiliser.

PRODUCT DESCRIPTION
Clear, colorless solution.

PHARMACOLOGY
The molecular weight of Recombinant Human Erythropoietin is approximately 30,000 Dalton. Sixty percent of the molecular weight is contributed by the protein fraction; this is made up of 185 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 human Erythropoietin producer cell strain. The recombinant producer cells strain is employed to produce the secretory product, which is purified to homogeneity.

PHARMACODYNAMICS
Erythropoietin is a mitosis stimulating glycoprotein hormone that stimulates circulatory and blood cell number. The efficacy of this compound has been demonstrated *in vivo* in different animal models (normal and anaemic rats, polycythemic mice). Following administration of this preparation, the erythrocyte counts, haemoglobin percent, reticulocyte counts and Fe-incorporation rates increase. Cultures of human bone marrow cells has shown that Erythropoietin stimulates the red blood cells specifically and does not affect white blood cell counts.

PHARMACOKINETICS
S.C. route: The serum concentrations of Erythropoietin obtained with subcutaneous injection are lower than with intravenous injection. The levels of 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. The bioavailability of Erythropoietin following subcutaneous injection is approximately 25%.
I.V. Route: The volume of distribution is similar to the plasma volume. When given by the intravenous route, the half-life is 5-8 hours, independent of the disease state.

CLINICAL INDICATIONS
Treatment of anaemia due to Erythropoietin deficiency in adult chronic renal failure patients and in predialysis, haemodialysis, peritoneal dialysis patients and in pediatric patients on haemodialysis. Treatment of anaemia in cancer patients with non-myeloid malignancies who are undergoing chemotherapy treatment. Treatment of anemia 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 hematocrits of 33-39%, who cannot produce the required blood without exogenous Erythropoietin. It is also 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. In these patients, it will reduce exposure to allergic blood transfusions and facilitate quick recovery of haemoglobin levels.

DOSAGE AND ADMINISTRATION
DOSAGE: Table for General Guidelines

INDICATION	INITIAL DOSE	MAINTENANCE DOSE
Chronic renal failure	50-100 IU/kg 3x/wk, IV/SC	Decrease the dose by 25 IU/kg/dose to maintain target hemoglobin
Adult predialysis patients	50-100 IU/kg 3x/wk, IV/SC	17-33 IU/kg 3x/wk
Adult hemodialysis patients	50-100 IU/kg 3x/wk, IV/SC	30-100 IU/kg 3x/wk
Adult peritoneal dialysis patient	50 IU/kg 2x/wk, SC	25-50 IU/kg 2x/wk
Pediatric hemodialysis patients	50 IU/kg 3x/wk, IV	Dose IU/kg 3x/wk Weight (kg) Maintenance <10 75-150 10-30 60-150 >30 30-100
Cancer patients	150 IU/kg 3x/wk, SC	If Hb concentration increases / mth (1) < 1g / dl - double the dose (2) > 2 g / dl - reduce dose by 25%
HIV infected patients on zidovudine	100 IU/kg 3x/wk for 8 wks SC, IV	
Adult surgery patients in an autologous pre donation program	600 IU/kg 2x/wk IV, for 3 wks prior to surgery	
Perisurgery patients without autologous blood donation	600 IU/kg once a wk SC for 3 wks prior to surgery or 300 IU/kg daily for 10 days before surgery and repeat on day of surgery, continue for 4 days after surgery	

DOSAGE: Details of Dosage
Chronic Renal Failure Patients - It 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. It is administered so as to maintain haemoglobin concentration between 11 to 12 g/dL or hematocrit 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 dose should be increased if the haemoglobin does not increase at least 1 g/dL/month or an increase in hematocrit 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 4 weeks until the required haemoglobin concentration is achieved. Maintenance Dose: The usual maintenance dose is 17 to 33 IU/kg thrice a week.

Acute Haemodialysis Patients - Initial Dose: 50 IU/kg is given thrice a week by subcutaneous or intravenous route. Dosage 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. Dosage 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.

Pediatric 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. Maintenance Dose: Children under 30 kg usually need higher maintenance doses than children over 30 kg and adults.

Dose (IU/kg 3x/week)

Weight (kg)	Median	Usual maintenance dose
<10	100	75-150
10-30	75	60-150
>30	33	30-100

Cancer Patients - The haemoglobin concentration needs to be maintained at 12 g/dL and the hematocrit at 36%. It is used for the treatment of symptomatic anaemia, to prevent anaemia in patients with haemoglobin levels < 11 g/dL prior to chemotherapy and patients who have shown a substantial decrease in haemoglobin in the first chemotherapy cycle (1.0 - 2.0 g/dL). The initial dose is 150 IU/kg thrice a week by the subcutaneous route. If following 4 weeks of treatment, the haemoglobin increase continues to be 1 g/dL, the dose is increased to 300 IU/kg for another 4 weeks. If after 4 weeks of treatment, the 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 hematocrit rises by > 4 points over a two week period, the 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 dose is resumed at a dose 25% lower than the previous dose.

The need of the Recombinant Human Erythropoietin therapy should be re-evaluated after completion of chemotherapy.

HIV Infected Patients on Zidovudine Treatment - The serum Erythropoietin serum level is determined prior to transfusion. Patients with serum Erythropoietin levels > 500 IU/mL are unlikely to respond to Recombinant Human Erythropoietin 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 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 dose of 300 IU/kg thrice a week, response at higher doses is unlikely.
Maintenance Dose: The dose is titrated to maintain the hematocrit between 33-36%. If the hematocrit exceeds 40%, the dose is withheld until the hematocrit falls to 36%. At resumption of treatment dose is reduced to 25% of the original dose.

Adult Surgery Patients in 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 Recombinant Human Erythropoietin IV twice a week. In some patient, a dose of 150- 300IU/kg given twice a week is found to be sufficient. It is generally given for three weeks prior to surgery. At each visit, one unit of blood is collected for autologous transfusion while maintaining the patient's hematocrit at 33% and haemoglobin > 11 g/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/kg recombinant human Erythropoietin is given daily for 10 days. The dose is repeated on the day of surgery and for four days after surgery.

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

TOXICOLOGY
Mutagenecity, Carcinogenicity and Impairment of Fertility - Erythropoietin does not induce bacterial gene mutation (Ames test), chromosomal aberrations in mammalian cells, micronuclei in mice, or gene mutation at the HGPRT locus. Carcinogenicity studies were not carried out. In rats and rabbits, when doses as large as 500 IU/Kg/day are given intravenously, there is no evidence of teratogenicity. Erythropoietin, when given intravenously, causes a slight but not statistically significant decrease in fertility.

WARNINGS

Chronic Kidney Disease:
- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.
- No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.

Use the lowest dose sufficient to reduce the need for red blood cell (RBC) transfusions.

Cancer:
- In clinical studies, ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.
- To decrease these risks, as well as the risk of serious cardiovascular and thromboembolic reactions, use the lowest dose needed to avoid RBC transfusions.
- Use ESAs only for anemia from myelosuppressive chemotherapy.

ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- Discontinue following the completion of a chemotherapy course.

Perisurgery:
Due to increased risk of Deep Venous Thrombosis (DVT), DVT prophylaxis is recommended.

Cautions
Increase incidence of death, myocardial infarction (MI), stroke, and thromboembolism: Using ESAs to target hemoglobin level of >11 g/dL increases risk of serious adverse cardiovascular reactions and has not been shown or provide additional benefit (see Black Box Warnings).
Use caution in hypertension, iron deficiency, folate or B12 deficiency, congestive heart failure (CHF), coronary artery disease (CAD),seizure disorder, sickle-cell, hemolytic anemia, porphyria, hematologic disorders.
Cancer patients: Increased tumor progression rate when dosed to achieve hemoglobin level of >12 mg/dL.
Chronic renal failure: At initiation of therapy, transferrin saturation should be ≥ 20 % and ferritin ≥ 100 ng/mL.
Patients undergoing surgery are at increased risk for DVT; concomitant DVT; concomitant DVT prophylaxis is strongly recommended.
Epoetin alfa multidose formulations contain benzyl alcohol, which is associated with potentially fatal " gasping syndrome" in premature neonates.
Zidovudine-treated patients may show response only when zidovudine dosage < 4200 mg/wk and endogenous epoetin < 500 U/mL.
To prescribe or dispense to patients with cancer and anemia due to myelosuppresive chemotherapy, prescribers and hospital must enroll in and comply with ESAAPPPRISE Oncology Program.
Increased risk of seizure during first 90 days of therapy in CKD; monitor closely.
Dialysis patients: IV administration recommended to reduce red-cell aplasia risk; increased anticoagulation with heparin may be required to prevent clotting of extracorporeal circuit during hemodialysis.
Do not increase dose more frequently than once monthly.
Contain albumin; may carry extremely remote risk for transmission or viral diseases or Creutzfeldt-Jakob disease.
Blistering and skin exfoliation reactions including erythema multiforme and Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN), reported in the post-marketing setting; discontinue therapy immediately if severe cutaneous reaction, such as SJS/TEN, is suspected.
Cases of PRCA and severe anemia, with or without other cytopenias that arise following the development of neutralizing antibodies to erthropoietin reported in patients treated with epoetin alfa.

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

ADVERSE DRUG REACTIONS
Hypertension is the most frequent occurring adverse reaction. Vascular events such as cerebrovascular accidents, transient ischemic attacks, aneurysms, deep venous thrombosis, myocardial infarction, pulmonary embolism and clotting of 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.

DRUG INTERACTIONS
No evidence exists that it alters the metabolism of other drugs. Blood levels of cyclosporine may need to be adjusted in patients on Recombinant Human Erythropoietin . Not to be diluted or transferred to another container. Not to be administered along with other drug solutions.

OVERDOSE AND TREATMENT
Recombinant Human Erythropoietin has a very wide safety margin. In cases of overdosage, 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 overdosage.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA:www.fda.gov.ph.
Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION
Store at temperatures between 2-8°C.
Protect from light.

AVAILABILITY
Single dose. USP Type I pre-filled glass syringe x 1 mL (Box of 1's)

BRP-109
Date of First Authorization: April 1, 2004
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M.L. AD/004

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