

R^x Recombinant Human Erythropoietin Injection

*ReliPoietin*TM

Prescribing Information

DESCRIPTION:

*ReliPoietin*TM (rHuEPO alpha) is a glycoprotein composed of 165 amino acids. It has a molecular weight of approximately 34 kDa. *ReliPoietin*TM is manufactured through Recombinant DNA technology. It uses mammalian cells into which an erythropoietin gene has been introduced. The proliferation, differentiation and maturation of red blood cells in the bone marrow are dependent on erythropoietin. In addition, the survival of RBC progenitors in bone marrow is influenced by erythropoietin. Erythropoietin also has immunomodulatory activity. The sequence of amino acids in *ReliPoietin*TM is exactly same as that in natural erythropoietin.

COMPOSITION:

*ReliPoietin*TM is a clear liquid. The aqueous preparation exists in phosphate buffer of pH 6.8 to 7.2 consisting of sodium phosphate, sodium chloride, glycine, polysorbate 20 and Erythropoietin concentrated solution Ph.Eur. The product is available in single use pre-filled syringes containing rHuEPO at different strengths and fill volumes as outlined below.

Product Strength	Nominal rHuEPO, Ph.Eur. Potency, Units/ mL	Nominal fill volume
<i>ReliPoietin</i> TM 2,000 IU	4,000	0.5 mL
<i>ReliPoietin</i> TM 3,000 IU	10,000	0.3 mL
<i>ReliPoietin</i> TM 4,000 IU	10,000	0.4 mL
<i>ReliPoietin</i> TM 6,000 IU	10,000	0.6 mL
<i>ReliPoietin</i> TM 10,000 IU	10,000	1.0 mL
<i>ReliPoietin</i> TM 40,000 IU	40,000	1.0 mL

PHARMACOLOGY:

Mechanism of Action:

rHuEPO is a glycoprotein which leads to the stimulation of red cell production. This hormone regulates the proliferation and differentiation of committed erythroid progenitors in the bone marrow. The release of reticulocytes is also accelerated by rHuEPO without altering the length of the cell cycle and the number of mitotic divisions involved in the differentiation process. It also increases the number of developing erythroid precursors in the bone marrow. This is followed by increase in red cell count, hemoglobin and hematocrit.

Pharmacokinetics:

Intravenously administered rHuEPO elimination follows 1st order kinetics with a circulating half life between 4 to 13 hours in adults and pediatric patients with chronic kidney disease. Within the therapeutic dose range, detectable levels of plasma erythropoietin are maintained for at least 24 hours. The peak serum levels are achieved within 5-24 hours and decline slowly after subcutaneous administration of rHuEPO. The half life did not vary significantly between adult patients not on dialysis with serum creatinine levels greater than 3 mg/dL and adult patient maintained on dialysis.

Toxicology:

Safety pharmacology, teratogenicity, mutagenicity and carcinogenicity studies were not done. Results of acute high single dose (2500 IU, 10000 IU/kg) toxicological studies conducted in dogs and rats for *ReliPoietin*TM showed no local intolerance and systemic toxicity. It indicated a reduction in percentage of reticulocytes at the end of observation period, which was a possible consequence of exhaustion of erythropoiesis following initial high stimulation.

INDICATIONS:

rHuEPO is used for:

- the treatment of anemia associated with chronic renal failure,
- in treatment of anemia in cancer patients on chemotherapy,
- in treatment of anemia in zidovudine-treated HIV affected patients, and
- in reduction of allogenic blood transfusions in surgery patients.

CONTRAINDICATIONS:

Patients with uncontrolled hypertension, having known hypersensitivity to mammalian cell derived products should not be administered rHuEPO.

ADVERSE EFFECTS:

Generally rHuEPO is well tolerated in humans. As with all therapeutic proteins, immunogenic potential can be experienced. There have been no reports of serious allergic or anaphylactic reactions along with rHuEPO therapy. Rarely mild transient rashes have been reported.

In clinical trials conducted, *ReliPoietin*TM was found to be safe and well tolerated. The non-serious adverse events reported were bilateral crepitations (4%), joint effusion (2.7%), peripheral oedema (2.7%), liver disorder (raised ALT in 2.7%), hypertension (1.3%), anxiety (1.3%), raised eosinophil counts (1.3%), dry skin (1.3%), and mouth ulceration (1.3%). The serious adverse events reported in the study were cardio-respiratory arrest, left ventricular failure, pulmonary oedema, lower respiratory tract infection and convulsion.

PRECAUTIONS:

The parenteral administration of rHuEPO should be attended carefully in the case of any anaphylactoid reactions. The safety and efficacy of rHuEPO therapy has not been established in patients with a known history of hematologic disease like sickle cell anemia, myelodysplastic syndrome and seizures. Before starting the medication, check if patient has high blood pressure, cancer, epilepsy, heart disease or any seizure disorder. In any of these conditions the patient may not be able to use rHuEPO or one may require a lower dose or special monitoring. The possibility of pregnancy should be discussed and contraception

should be used if needed. rHuEPO is categorized in FDA pregnancy category C. It is not known whether rHuEPO shall harm an unborn baby or not. It is also not known whether rHuEPO passes into the breast milk or not.

WARNING:

A warning for all other erythropoiesis-stimulating-agents (ESA) is applicable to erythropoietin. *ReliPoietin*TM like other ESAs poses an increased risk of serious cardiovascular and thromboembolic events, tumor progression and death when administered to achieve hemoglobin level greater than 12 g/dL. Due care should be taken while treating patients with rHuEPO.

DRUG INTERACTIONS:

No formal drug interaction studies of rHuEPO with other medications commonly used in cancer patients on chemotherapy, CRF patients and AIDS patients have been fully studied.

OVERDOSAGE:

The maximum dose of rHuEPO to be administered in single or multiple doses has not been determined. There have been no direct toxic effects observed of doses up to 1500 units/kg TIW of rHuEPO given for 3-4 weeks. If hematocrit is not monitored carefully and dose adjustment is not done accordingly then rHuEPO therapy can result in polycythemia. The rHuEPO therapy should be temporarily withheld if suggested level of hemoglobin and/or target range of hematocrit is reached. Supportive care should be provided depending on the symptoms of overdosage. Later on, if need be, the rHuEPO therapy may be resumed using a lower dose.

DOSAGE AND ADMINISTRATION:

For chronic renal failure patients:

The recommended range of starting dose of rHuEPO is 50 - 100 units/ kg, 2-3 doses weekly for up to 8 weeks. rHuEPO is administered as intravenous or subcutaneous injections. The dose should be reduced as hemoglobin level approaches 12g/dL. The maintenance dose for CRF patients should be individualized. The median maintenance dose is 75 units/kg TIW.

For cancer patients on chemotherapy:

The starting dose of rHuEPO is 150 units/kg TIW, given intravenously or subcutaneously. After 8 weeks of therapy if the response is not satisfactory in terms of reducing transfusions or increasing hematocrit, the dose of rHuEPO can be increased to 300 units/kg TIW. If the patients have not responded to 300 units/kg of rHuEPO it is unlikely that they will respond to higher doses of rHuEPO. If the hematocrit exceeds 40%, the dose of rHuEPO should be withheld until hematocrit falls to 36%. Subsequent to this, treatment with rHuEPO is resumed at 25% lesser dose and titrated to maintain the desired hematocrit. If the initial dose of rHuEPO indicates a very rapid hematocrit response (e.g. an increase of more than 2 percentage points in any 1 week period) the dose of rHuEPO should be reduced.

For zidovudine treated HIV infected patients:

Before starting the rHuEPO therapy, it is suggested to determine the endogenous serum erythropoietin levels as evidence suggests that patients receiving zidovudine with endogenous serum erythropoietin levels > 500 m Units/mL are unlikely to respond to rHuEPO.

Starting Dose

For adult patients a dose of 100 units/kg intravenously or subcutaneously, TIW, for 8 weeks is recommended in whom serum erythropoietin levels are < 500 m Units/mL and who are receiving zidovudine at a dose of < 4,200 mg/week.

Dose Titration

Hematocrit should be monitored weekly during the adjustment phase of the therapy. The dose of rHuEPO can be increased by 50-100 units/kg, if response is not satisfactory in terms of reducing transfusion requirements or increasing hematocrit after 8 weeks of therapy. The evaluation of response should be done every 4-8 weeks thereafter and the dose should be adjusted accordingly. If there is no satisfactory response to 300 units/kg TIW of rHuEPO therapy, it is unlikely that those patients will respond to higher doses of rHuEPO.

Maintenance Dose

When the desired response has been achieved i.e. reduced need of transfusions or increased hematocrit, the dose of rHuEPO should be titrated to maintain the response based on the factors such as variations in zidovudine dose and presence of intercurrent infectious or inflammatory episodes. If the hematocrit exceeds the level of 40%, the rHuEPO treatment should be discontinued until hematocrit reaches 36%. The dose should be reduced by 25% when treatment is resumed and titration should be done to maintain desired hematocrit.

In surgery patients to reduce transfusions: (For non-cardiac and non-vascular surgeries)

Before beginning the rHuEPO therapy the hemoglobin level should be measured to establish that it is > 10 to < 13 g/dL. The recommended dose of rHuEPO is 300 units/Kg/day subcutaneously for 10 days before surgery, on the day of surgery and 4 days after surgery. Another dosage schedule is 600 units/kg rHuEPO subcutaneously in once weekly doses (on 21st, 14th and 7th day before surgery) plus a fourth dose on the day of surgery. All patients should receive iron supplementation. Iron supplementation should be initiated along with the treatment with rHuEPO and should continue throughout the course of therapy.

PRESENTATION:

*ReliPoietin*TM is available as Pre-Filled Syringes for single use, containing either 2000, 3000, 4000, 6000, 10000, or 40000 IU of Erythropoietin concentrated solution Ph.Eur.

STORAGE:

Store between 2°C and 8°C. Do not freeze or shake.

The shelf life of the single dose Pre-filled syringe is two years from the date of manufacturing.

