For the use of registered medical practitioner, hospital or laboratory only.

ERYKINE

Erythropoietin Injection BP
Recombinant Human Erythropoietin Injection

Each prefilled syringe of 1.0 ml contains:
Erythropoietin Concentrated Solution BP 2000IU
Each prefilled syringe of 1.0 ml contains:
Erythropoietin Concentrated Solution BP 4000 IU

Description

Erythropoietin is a glycoprotein, which stimulates red blood cell production. It is produced in the kidney and stimulates the division and differentiation of committed erythroid progenitors in the bone marrow. Recombinant Human erythropoietin (Epoetin alfa), a 165 amino acid glycoprotein manufactured by recombinant DNA technology, has the same biological effects as endogenous erythropoietin. It has a molecular weight of 30,400 daltons and is produced by mammalian cells into which the human erythropoietin gene has been introduced. The product contains the identical amino acid sequence of isolated natural erythropoietin.

Erykine (erythropoietin injection BP) is a clear, colorless, preservative free liquid containing active ingredient erythropoietin alpha.

(a) Erythropoietin concentrated solution BP	2000 IU	(b) Erythropoietin concentrated solution BP	4000 IU
Human Serum Albumin	2.5 mg	Human Serum Albumin	2.5 mg
Sodium citrate	5.8 mg	Sodium citrate	5.8 mg
Sodium chloride	5.8 mg	Sodium chloride	5.8 mg
Citric acid	0.06 mg	Citric acid	0.06 mg
Water for injection	1.0 ml	Water for injection	1.0 ml

Preclinical Pharmacology:

Invivo bioassay was performed to assess the potency of erythropoietin Erykine in swiss albino mice based on European Pharmacopoeia requirements. Reticulocyte count was analyzed using parallel line assay. The analysis revealed that the Intas erythropoietin (Erykine) and the standard erythropoietin are comparable in specific biological activities.

Toxicity Studies:

Acute toxicity studies were conducted in rats and mice by administering Erykine by I. V. and S. C. routes in a single dose of 3000 IU/kg. There was no death or any abnormality in gross organ examinations in both the species. In repeat dose subacute toxicity studies in rats and mice a dose of 30, 300, 3000 IU/kg was administered for a period of 28 days by SC and IV routes. The animals were examined for body weight changes, food consumption, hematology, blood chemistry and histopathological examination of body organs. There was no abnormality detected in any of the parameters in both the species. Erykine was well tolerated in low, medium and high dose levels in these studies.

Erykine was also evaluated for local irritation and allergencity by conducting primary irritation test in rabbits and allergic contact sensitization in guinea pigs. The test drug was well tolerated and there was no evidence of any irritation or sensitization in the animals.

Clinical Pharmacology:

Chronic Renal Failure Patients:

Endogenous production of erythropoietin is normally regulated by the level of tissue oxygenation. Hypoxia and anemia generally increase the production of erythropoietin, which in turn stimulates erythropoiesis. In normal subjects, plasma erythropoietin levels range from 0.01 to 0.03 Units/mL and increase up to 100- to 1000-fold during hypoxia or anemia. In contrast, in patients with chronic renal failure (CRF), production of erythropoietin is impaired, and this erythropoietin deficiency is the primary cause of their anemia.

Erythropoietin has been shown to stimulate erythropoiesis in anemic patients with CRF, including both patients on dialysis and those who do not require regular dialysis. The first evidence of a response to the three times weekly (TIW) administration of erythropoietin is an increase in the reticulocyte count within 10 days, followed by increases in the red cell count, hemoglobin, and hematocrit, usually within 2 to 6 weeks. Once the hematocrit reaches the suggested target range (30% to 36%), that level can be sustained by erythropoietin therapy in the absence of iron deficiency and concurrent illnesses.

The rate of hematocrit increase varies between patients and is dependent upon the dose of erythropoietin, within a therapeutic range of approximately 50 to 300 Units/kg. The factors affecting the rate and extent of response include availability of iron stores, the baseline hematocrit, and the presence of concurrent medical problems.

Cancer Patients on Chemotherapy

Anemia in cancer patients may be related to the disease itself or the effect of concomitantly administered chemotherapeutic agents. Erythropoietin has been shown to increase hematocrit and decrease transfusion requirements after the first month of therapy (months 2 and 3), in anemic cancer patients undergoing chemotherapy.

Zidovudine-treated HIV-infected Patients

Responsiveness to erythropoietin in HIV-infected patients is dependent upon the endogenous serum erythropoietin level prior to treatment. Patients with endogenous serum erythropoietin levels = 500 mUnits/mL, and who are receiving a dose of zidovudine <= 4200 mg/week, may respond to erythropoietin therapy. Patients with endogenous serum

erythropoietin levels > 500 mUnits/mL do not appear to respond to erythropoietin therapy.

Response to erythropoietin in zidovudine-treated HIV-infected patients is manifested by reduced transfusion requirements and increased hematocrit.

Pharmacokinetics

Intravenously administered erythropoietin is eliminated at a rate consistent with first order kinetics with a circulating half-life ranging from approximately 4 to 13 hours in adult and pediatric patients with CRF. Within the therapeutic dose range, detectable levels of plasma erythropoietin are maintained for at least 24 hours. After SC administration of erythropoietin to patients with CRF, peak serum levels are achieved within 5 to 24 hours after administration and decline slowly thereafter.

The pharmacokinetic profile of erythropoietin in children and adolescents appears to be similar to that of adults. Limited data are available in neonates.

Clinical Effects:

Chronic Renal Failure Patients:

Response to erythropoietin was consistent across all studies. In the presence of adequate iron stores (see Iron Evaluation), the time to reach the target hematocrit is a function of the baseline hematocrit and the rate of hematocrit rise.

The rate of increase in hematocrit is dependent upon the dose of erythropoietin administered and individual patient variation.

Once the target hematocrit (32% to 38%) was achieved, statistically significant improvements were demonstrated for most quality of life parameters measured, including energy and activity level, functional ability, sleep and eating behavior, health status, satisfaction with health, sex life, well-being, psychological effect, life satisfaction, and happiness.

Adult Patients on Dialysis:

The clinical studies were conducted, involving IV administration of erythropoietin to anemic patients on dialysis. In the three largest of these clinical trials, the median maintenance dose necessary to maintain the hematocrit between 30% to 36% was approximately 75 Units/kg TIW.

Patients With CRF Not Requiring Dialysis

The clinical trials with erythropoietin were conducted in patients with CRF not on dialysis. The patients responded to erythropoietin therapy in a manner similar to that observed in patients on dialysis. Patients with CRF not on dialysis demonstrated a dose-dependent and sustained increase in hematocrit when erythropoietin was administered by either an IV or SC route, with similar rates of rise of hematocrit when erythropoietin was administered by either route.

Zidovudine-treated HIV-infected Patients

Erythropoietin has been studied in clinical trials enrolling anemic (hematocrit < 30%) HIV-infected (AIDS) patients receiving concomitant therapy with zidovudine. Erythropoietin reduced the mean cumulative number of units of blood transfused per patient by approximately 40% as compared to the placebo group.

In a 6 month open-label erythropoietin study, patients responded with decreased transfusion requirements and sustained increases in hematocrit and hemoglobin with doses of erythropoietin up to 300 Units/kg TIW.

Cancer Patients on Chemotherapy

Erythropoietin has been studied in a series of placebo-controlled, double blind trials in anemic cancer patients. Within this group, patients were treated with concomitant non cisplatin-containing chemotherapy regimens and cisplatin-containing chemotherapy regimens. Patients were randomized to erythropoietin 150 Units/kg or placebo subcutaneously TIW for 12 weeks.

Erythropoietin therapy was associated with a significantly ($p < 0.008$) greater hematocrit response than in the corresponding placebo-treated patients

Surgery Patients

Erythropoietin has been studied in a placebo-controlled, double-blind trial enrolling patients scheduled for major, elective orthopedic hip or knee surgery who were expected to require >= 2 units of blood and who were not able or willing to participate in an autologous blood donation program. All patients received oral iron and a low-dose post-operative warfarin regimen.

Treatment with erythropoietin 300 Units/kg significantly ($p = 0.024$) reduced the risk of allogeneic transfusion in patients with a pretreatment hemoglobin of > 10 to <= 13 g/dL.

Efficacy of Erykine in Indian Patients:

The efficacy and safety of Erykine was evaluated in open label, 12 weeks, phase III confirmatory trial conducted in Indian patients for the treatments of anemia due to chronic kidney disease. This multicentre study enrolled patients both on dialysis and those not on dialysis with a hematocrit of ≤ 24%. Patients were evaluated for rise in hematocrit and reticulocyte count after Erykine administration at the baseline and 2- weeks. The patients were also evaluated for achieving the target hematocrit > 33% at 12 weeks of drug administration in a dose of 50-150 IU/kg three times in a week. The safety of Erykine was assessed by reporting spontaneous and serious adverse events and laboratory investigations for liver and kidney functions.

There was significant mean increase in hematocrit of 2.63% and reticulocyte of 1.07% (corrected for hematocrit) after 2 weeks of drug administration. 63.2% of patients achieved the target hematocrit of 33% or more at 12 weeks of Erykine administration. The remaining

36.8% patients showed an increase in hematocrit till the end of study. No patients required blood transfusion during the treatment with Erykine. There was no alteration in liver and kidney functions after Erykine administration as assessed by laboratory investigations. The drug was well tolerated in all the patients and no significant adverse effects reported with Erykine in this study.

Indications And Usage:

Anemia Associated with Chronic Renal Failure in Hemodialysis in Adults, on Peritoneal Dialysis and Non-dialysis Adults.

Erythropoietin is indicated for the treatment of anemia associated with CRF, including patients on dialysis (ESRD) and patients not on dialysis. Erythropoietin is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients.

Contraindications:

Erythropoietin is contraindicated in patients with:

1. Uncontrolled hypertension.
2. Known hypersensitivity to mammalian cell-derived products.
3. Known hypersensitivity to Albumin (Human).

Warnings:

Thrombotic Events and Increased Mortality:

Increased mortality was observed in patients randomized to a target hematocrit of 42% [(35% mortality)] compared to patients targeted to remain at a hematocrit of 30% [(29% mortality)].

***Chronic Renal Failure Patients*:**

Hypertension: Patients with uncontrolled hypertension should not be treated with erythropoietin; blood pressure should be controlled adequately before initiation of therapy. During the early phase of treatment when the hematocrit is increasing, approximately 25% of patients on dialysis may require initiation of, or increases in, antihypertensive therapy. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with erythropoietin

Seizures: Seizures have occurred in patients with CRF participating in erythropoietin clinical trials. It is recommended that the dose of erythropoietin be decreased if the hematocrit increase exceeds 4 points in any 2-week period.

Thrombotic Events: During hemodialysis, patients treated with erythropoietin may require increased anticoagulation with heparin to prevent clotting of the artificial kidney.

Precautions:

The parenteral administration of any biologic product should be attended by appropriate precautions in case allergic or other untoward reactions occur in clinical trials, while transient rashes were occasionally observed concurrently with erythropoietin therapy; no serious allergic or anaphylactic reactions were reported.

The safety and efficacy of erythropoietin therapy have not been established in patients with a known history of a seizure disorder or underlying hematologic disease (eg, sickle cell anemia, myelodysplastic syndromes, or hypercoagulable disorders).

Hematology: Exacerbation of porphyria has been observed rarely in patients with CRF treated with erythropoietin. Erythropoietin should be used with caution in patients with known porphyria.

Delayed or Diminished Response

If the patient fails to respond or to maintain a response to doses within the recommended dosing range, the following etiologies should be considered and evaluated:

- Iron deficiency: Virtually all patients will eventually require supplemental iron therapy
- Underlying infectious, inflammatory, or malignant processes.
- Occult blood loss.
- Underlying hematologic diseases (ie, thalassemia, refractory anemia, or other myelodysplastic disorders).
- Vitamin deficiencies: Folic acid or vitamin B12.
- Hemolysis.
- Aluminum intoxication.
- Osteitis fibrosa cystica.

Iron Evaluation

Transferrin saturation should be at least 20% and ferritin should be at least 100 ng/mL.

Prior to and during erythropoietin therapy, the patient's iron status, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels, which will adequately support erythropoiesis stimulated by erythropoietin.

Drug Interaction:

No evidence of interaction of erythropoietin with other drugs was observed in the course of clinical trials.

Carcinogenesis, Mutagenesis, And Impairment Of Fertility:

Carcinogenic potential of erythropoietin has not been evaluated. Erythropoietin does not induce bacterial gene mutation (Ames Test), chromosomal aberrations in mammalian cells, micronuclei in mice, or gene mutation at the HGPRT locus. In female rats treated IV with erythropoietin, there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg.

Pregnancy:

Pregnancy Category C:

There are no adequate and well-controlled studies in pregnant women. Erythropoietin should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether erythropoietin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when erythropoietin is administered to a nursing woman.

Chronic Renal Failure Patients

Patients with CRF Not Requiring Dialysis:

Blood pressure and hematocrit should be monitored no less frequently than for patients maintained on dialysis.

Hematology:

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of erythropoietin before adjusting the dose because of the time required for erythropoiesis and the red cell half-life, an interval of 2 to 6 weeks may occur between the time of a dose adjustment (initiation, increase, or decrease, or discontinuation) and a significant change in hematocrit.

Laboratory Monitoring:

The hematocrit should be determined twice a week until it has stabilized in the suggested target range and the maintenance dose has been established. The hematocrit should then be monitored at regular intervals.

A complete blood count with differential and platelet count should be performed regularly. During clinical trials, modest increases were seen in platelets and white blood cell counts. While these changes were statistically significant, they were not clinically significant and the values remained within normal ranges.

In patients with CRF, serum chemistry values (including blood urea nitrogen [BUN], uric acid, creatinine, phosphorus, and potassium) should be monitored regularly.

Diet:

As the hematocrit increases and patients experience an improved sense of well-being and quality of life, the importance of compliance with dietary and dialysis prescriptions should be reinforced. In particular, hyperkalemia is not uncommon in patients with CRF.

Dialysis Management:

Therapy with erythropoietin results in an increase in hematocrit and a decrease in plasma volume, which could affect dialysis efficiency. During hemodialysis, patients treated with erythropoietin may require increased anticoagulation with heparin to prevent clotting of the artificial kidney.

Renal Function:

In adult patients with CRF not on dialysis, renal function and fluid and electrolyte balance should be closely monitored, as an improved sense of well-being may obscure the need to initiate dialysis in some patients.

Adverse Reactions:

Erythropoietin is generally well tolerated. The adverse events reported are frequent sequelae of disease and are not necessarily attributable to erythropoietin therapy. The events reported in greater than 5% of patients treated with erythropoietin during the blinded phase were: hypertension, headache, arthralgia, nausea, edema, fatigue, diarrhea, vomiting, chest pain, skin reaction (administration site), asthenia, dizziness, clotted access, pyrexia, constipation, deep vein thrombosis. Events reported to have occurred within several hours of administration of erythropoietin were rare, mild, and transient, and included injection site stinging in dialysis patients and flu-like symptoms such as arthralgias and myalgias.

Overdosage:

The maximum amount of erythropoietin that can be safely administered in single or multiple doses has not been determined. Doses of up to 1500 Units/kg TIW for 3 to 4 weeks have been administered to adults without any direct toxic effects of erythropoietin.

Dosage And Administration:

1. Anemia Associated with Chronic Renal Failure.

The recommended range for the starting dose of erythropoietin is 50 to 100 Units/kg TIW for adult patients. The dose of erythropoietin should be reduced as the hematocrit approaches 36% or increases by more than 4 points in any 2-week period.

Erythropoietin may be given either as an IV or SC injection.

During therapy, hematological parameters should be monitored regularly Dose adjustment should not be made more frequently than once a month, unless clinically indicated.

Preparation And Administration of erythropoietin:

Do not shake as vigorous shaking may denature any glycoprotein, rendering it biologically inactive. Use aseptic techniques in drug administration. Use one dose pre-filled syringe. Discard unused portion, do not dilute or administer in conjunction with other solutions.

How Supplied

Erykine is available in 1 ml prefilled syringes containing 2000 IU and 4000 IU of recombinant human erythropoietin.

Storage

Store at 2° to 8°C (36° to 46°F). Do not freeze or shake.

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