Ropo™ Injection
(Erythropoietin)

For subcutaneous or intravenous use only

DESCRIPTION:
Ropo™ (Erythropoietin) is a 165-amino acid erythropoiesis-stimulating glycoprotein manufactured by recombinant DNA technology. It 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. Ropo™ is formulated as a sterile, colorless liquid formulation in pre-filled syringe

COMPOSITION:

Ropo™ 2000 IU Injection:	Ropo™ 4000 IU Injection:	Ropo™ 10,000 IU Injection:
Each 1.0ml Pre-filled syringe contains:	Each 1.0ml Pre-filled syringe contains:	Each 1.0ml Pre-filled syringe contains:
Erythropoietin .....2000 IU	Erythropoietin .....4000 IU	Erythropoietin .....10,000 IU

CLINICAL PHARMACOLOGY:
Mechanism of action: Erythropoietin stimulates erythropoiesis by the same mechanism as endogenous erythropoietin

Pharmacodynamics: Erythropoietin increases the reticulocyte count within 10 days of initiation, followed by increases in the RBC count, hemoglobin, and hematocrit, usually within 2 to 6 weeks. The rate of hemoglobin increase varies among patients and is dependent upon the dose of erythropoietin administered. For correction of anemia in hemodialysis patients, a greater biologic response is not observed at doses exceeding 300 units/kg 3 times weekly

Pharmacokinetics: In adult and paediatric patients with CKD, the elimination half-life ($t_{1/2}$) of plasma erythropoietin after intravenous administration of erythropoietin ranged from 4 to 13 hours. After subcutaneous administration, C_{max} was achieved within 5 to 24 hours. The $t_{1/2}$ in adult patients with serum creatinine greater than 3mg/dL was similar between those not on dialysis and those maintained on dialysis. The pharmacokinetic data indicate no apparent difference in erythropoietin $t_{1/2}$ among adult patients above or below 65 years of age

The pharmacokinetic profile of erythropoietin in children and adolescents is similar to that of adults

The pharmacokinetics of erythropoietin has not been studied in patients with HIV infection

INDICATIONS AND USAGE:
Anemia due to Chronic Kidney Disease: Erythropoietin is indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion

Anemia due to Zidovudine in HIV-infected patients: Erythropoietin is indicated for the treatment of anemia due to zidovudine administered at < 4200mg/week in HIV-infected patients with endogenous serum erythropoietin levels of < 500 mUnits/mL

Anemia due to chemotherapy in patients with cancer: Erythropoietin is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy

Reduction of Allogeneic Red Blood Cell transfusions in patients undergoing Elective, Noncardiac, Nonvascular Surgery: Erythropoietin is indicated to reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin > 10 to < 13g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery. Erythropoietin is not indicated for patients who are willing to donate autologous blood preoperatively

Limitations of use: Erythropoietin has not been shown to improve quality of life, fatigue, or patient well-being
Erythropoietin is not indicated for use:
- In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure
- In patients scheduled for surgery who are willing to donate autologous blood
- In patients undergoing cardiac or vascular surgery

As a substitute for RBC transfusions in patients who require immediate correction of anemia

DOSAGE AND ADMINISTRATION:
Evaluation of iron stores and nutritional factors: Evaluate the iron status in all patients before and during treatment and maintain iron repletion. Correct or exclude other causes of anemia (e.g., vitamin deficiency, metabolic or chronic inflammatory conditions, bleeding, etc.) before initiating erythropoietin

Patients with Chronic Kidney Disease: When initiating or adjusting therapy, monitor hemoglobin levels at least weekly until stable, then monitor at least monthly. When adjusting therapy consider hemoglobin rate of rise, rate of decline, ESA responsiveness and hemoglobin variability. A single hemoglobin excursion may not require a dosing change
- Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently. Avoid frequent dose adjustments
- If the hemoglobin rises rapidly (e.g. more than 1g/dL in any 2-week period), reduce the dose of erythropoietin by 25% or more as needed to reduce rapid responses
- For patients who do not respond adequately, if the hemoglobin has not increased by more than 1g/dL after 4 weeks of therapy, increase the dose by 25%
- For patients who do not respond adequately over a 12-week escalation period, increasing the erythropoietin dose further is unlikely to improve response and may increase risks. Use the lowest dose that will maintain a hemoglobin level sufficient to reduce the need for RBC transfusions. Evaluate other causes of anemia. Discontinue erythropoietin if responsiveness does not improve

For patients with CKD on dialysis:
- Initiate erythropoietin treatment when the hemoglobin level is less than 10g/dL
- If the hemoglobin level approaches or exceeds 11g/dL, reduce or interrupt the dose of erythropoietin
- The recommended starting dose for adult patients is 50 to 100 units/kg 3 times weekly intravenously or subcutaneously. For paediatric patients, a starting dose of 50 units/kg 3 times weekly intravenously or subcutaneously is recommended. The intravenous route is recommended for patients on hemodialysis

For patients with CKD not on dialysis:
- Consider initiating erythropoietin treatment only when the hemoglobin level is less than 10g/dL and the following considerations apply:
  - The rate of hemoglobin decline indicates the likelihood of requiring a RBC transfusion and
  - Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal
- If the hemoglobin level exceeds 10g/dL, reduce or interrupt the dose of erythropoietin , and use the lowest dose of erythropoietin sufficient to reduce the need for RBC transfusions
- The recommended starting dose for adult patients is 50 to 100 units/kg 3 times weekly intravenously or subcutaneously

When treating patients who have chronic kidney disease and cancer, physicians should refer to "Warnings and Precautions"

Zidovudine-treated HIV-infected patients
Starting Dose: The recommended starting dose in adults is 100 units/kg as an intravenous or subcutaneous injection 3 times per week

Dose Adjustment
- If hemoglobin does not increase after 8 weeks of therapy, increase erythropoietin dose by approximately 50 to 100 units/kg at 4 to 8 week intervals until hemoglobin reaches a level needed to avoid RBC transfusions or 300 units/kg
- Withhold erythropoietin if hemoglobin exceeds 12g/dL. Resume therapy at a dose 25% below the previous dose when hemoglobin declines to less than 11g/dL

Discontinue erythropoietin if an increase in hemoglobin is not achieved at a dose of 300 units/kg for 8 weeks

Patients on cancer chemotherapy: Initiate erythropoietin in patients on cancer chemotherapy only if the hemoglobin is less than 10g/dL, and if there is a minimum of two additional months of planned chemotherapy. Use the lowest dose of erythropoietin necessary to avoid RBC transfusions

Recommended starting dose
Adults:
- 150 units/kg subcutaneously 3 times per week until completion of a chemotherapy course OR
- 40,000 units subcutaneously weekly until completion of a chemotherapy course

Paediatric patients (5 to 18 years):
- 600 units/kg intravenously weekly until completion of a chemotherapy course

Dose reduction: Reduce dose by 25% if:
- Hemoglobin increases greater than 1g/dL in any 2-week period OR
- Hemoglobin reaches a level needed to avoid RBC transfusion

Withhold dose if hemoglobin exceeds a level needed to avoid RBC transfusion. Reinitiate at a dose 25% below the previous dose when hemoglobin approaches a level where RBC transfusions may be required

Dose increase: After the initial 4 weeks of erythropoietin therapy, if hemoglobin increases by less than 1g/dL and remains below 10g/dL, increase dose to:
- 300 units/kg three times per week in adults OR
- 60,000 units weekly in adults
- 900 units/kg (maximum 60,000 units) weekly in children

After 8 weeks of therapy, if there is no response as measured by hemoglobin levels or if RBC transfusions are still required, discontinue erythropoietin

Surgery patients: The recommended erythropoietin regimens are:
- 300 units/kg per day subcutaneously for 15 days total: Administered daily for 10 days before surgery, on the day of surgery, and for 4 days after surgery
- 600 units/kg subcutaneously in 4 doses administered 21, 14, and 7 days before surgery and on the day of surgery

Deep venous thrombosis prophylaxis is recommended during erythropoietin therapy

CONTRAINDICATIONS:
Erythropoietin is contraindicated in patients with:
- Uncontrolled hypertension
- Pure red cell aplasia (PRCA) that begins after treatment with erythropoietin or other erythropoietin protein drugs
- Serious allergic reactions to erythropoietin

WARNINGS AND PRECAUTIONS:
- Increased Mortality, Myocardial Infarction, Stroke and Thromboembolism: Using ESAs to target a hemoglobin level of greater than 11g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit. Use caution in patients with coexistent cardiovascular disease and stroke
- Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients With Cancer
- Hypertension: Control hypertension prior to initiating and during treatment with erythropoietin
- Seizures: Erythropoietin increases the risk for seizures in patients with CKD. Increase monitoring of these patients for changes in seizure frequency or premonitory symptoms
- Pure red cell aplasia (PRCA): If severe anemia and low reticulocyte count develop during erythropoietin treatment, withhold erythropoietin and evaluate for PRCA

ADVERSE REACTIONS:
- Patients with CKD: Adverse reactions in > 5% of erythropoietin-treated patients in clinical studies were hypertension, arthralgia, muscle spasm, pyrexia, dizziness, medical device malfunction, vascular occlusion, and upper respiratory tract infection
- Zidovudine-treated HIV-infected patients: Adverse reactions in > 5% of erythropoietin-treated patients in clinical studies were pyrexia, cough, rash, and injection site irritation
- Cancer patients on chemotherapy: Adverse reactions in > 5% of erythropoietin treated patients in clinical studies were nausea, vomiting, myalgia, arthralgia, stomatitis, cough, weight decrease, leukopenia, bone pain, rash, hyperglycemia, insomnia, headache, depression, dysphagia, hypokalemia, and thrombosis
- Surgery patients: Adverse reactions in > 5% of erythropoietin-reated patients in clinical studies were nausea, vomiting, pruritus, headache, injection site pain, chills, deep vein thrombosis, cough, and hypertension

DRUG INTERACTIONS:
No formal drug interaction studies have been conducted with erythropoietin

USE IN SPECIFIC POPULATIONS:
Pregnancy Category C: Erythropoietin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing mothers: It is not known whether erythropoietin is excreted in human milk, hence caution should be exercised when erythropoietin is administered to a nursing woman

Paediatric use: When therapy with erythropoietin is needed in neonates and infants, use a benzyl alcohol-free formulation, as benzyl alcohol has been associated with serious adverse events and death, particularly in paediatric patients

Paediatric patients on dialysis: Erythropoietin is indicated in paediatric patients, ages 1 month to 16 years of age, for the treatment of anemia associated with CKD requiring dialysis. Safety and effectiveness in paediatric patients less than 1 month old have not been established

Paediatric cancer patients on chemotherapy: Erythropoietin is indicated in patients 5 to 18 years old for the treatment of anemia due to concomitant myelosuppressive chemotherapy. Safety and effectiveness in paediatric patients less than 5 years of age have not been established

Geriatric use: There are no differences in safety or effectiveness between geriatric and younger patients. Dose selection and adjustment for an elderly patient should be individualized to achieve and maintain the target hemoglobin

OVERDOSAGE:
Erythropoietin overdosage can cause hemoglobin levels above the desired level, which should be managed with discontinuation or reduction of erythropoietin dosage and/or with phlebotomy, as clinically indicated

STABILITY:
See expiry on the pack

AVAILABILITY:
Ropo™ 2000 units/1ml pre-filled syringe in a pack of 1's
Ropo™ 4000 units/1ml pre-filled syringe in a pack of 1's
Ropo™ 10,000 units/1ml pre-filled syringe in a pack of 1's

INSTRUCTIONS:
Do not shake. PFS is a single dose should be used only one time
Keep out of reach of children
Avoid exposure to heat, light and freezing
Store at 2 to 8°C
Improper storage may deteriorate the medicine

Caution: Injection should not be used if PFS is leaking, solution is discolor, cloudy or it contains undissloved particle(s)

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com

روپو™ انجکشن
(اریتھروپوئیٹن)

PFS کو ہلانے سے گریز کریں اور صرف ایک دفعہ استعمال کریں

خوراک اور طریقہ استعمال: ڈاکٹر کی ہدایت کے مطابق استعمال کریں

بچوں کی پہنچ سے دور رکھیں

دوا کو دھوپ، گرمی اور منجمد ہونے سے محفوظ ۲ سے ۸ ڈگری سینٹی گریڈ پر رکھیں
ورنہ دوا خراب ہو جائیگی

احتیاط: PFS کے لیک ہونے، محلول کا رنگ تبدیل ہونے، دُھندلا ہونے یا
اس میں کوئی غیر حل پذیر شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں