neurologic symptoms should be monitored closely. Patients should be cautioned to avoid potentially hazardous activities such as driving or operating heavy machinery during this period. It is recommended that the dose of erythropoietin be decreased if the hemoglobin increase exceeds 1 g/dL in any 2-week period.

Lack or loss of hemoglobin response to erythropoietin: For lack or loss of hemoglobin response to erythropoietin, initiate a search for causative factors (e.g., iron deficiency, infection, inflammation, bleeding). If typical causes of lack or loss of hemoglobin response are excluded, evaluate for PRCA. In the absence of PRCA, follow dosing recommendations for management of patients with an insufficient hemoglobin response to erythropoietin therapy.

Serious allergic reactions: Serious allergic reactions, including anaphylactic reactions, angioedema, bronchospasm, skin rash, and urticaria may occur with erythropoietin. Immediately and permanently discontinue erythropoietin and administer appropriate therapy if a serious allergic or anaphylactic reaction occurs.

Dialysis management: Patients may require adjustments in their dialysis prescriptions after initiation of erythropoietin. Patients receiving erythropoietin may require increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis.

Laboratory monitoring: Evaluate transferrin saturation and serum ferritin prior to and during erythropoietin treatment. Administer supplemental iron therapy when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20%. The majority of patients with CKD will require supplemental iron during the course of ESA therapy. Following initiation of therapy and after each dose adjustment, monitor hemoglobin weekly until the hemoglobin level is stable and sufficient to minimize the need for RBC transfusion.

ADVERSE EFFECTS

Following are the adverse events seen with erythropoietin.
Cardiovascular: Chest pain, congestive cardiac failure, edema, hypertension, myocardial infarction, tachycardia.
Dermatological: Diaphoresis, injection site reaction, pain of skin, pruritus, rash.
Gastrointestinal: Constipation, diarrhea, indigestion, nausea, vomiting.
Hematologic: Severe anemia, deep venous thrombosis, injection site thrombosis, porphyria, exacerbation, pure red cell aplasia, venous thromboembolism.
Immunologic: Anaphylaxis, antibody development, immune hypersensitivity reaction.
Musculoskeletal: Arthralgia.
Neurological: Aphasia, cerebral ischemia, cerebrovascular accident, transient ischemic attack, dizziness, headache, hypertensive encephalopathy, insomnia, paresthesia, seizure.
Ophthalmic: Conjunctivitis, thrombosis of retinal artery.
Psychiatric: Anxiety.
Renal: Nephrotoxicity, thrombosis of renal vein, urinary tract infectious disease.
Respiratory: Cough, dyspnea, pulmonary congestion, upper respiratory infection.
Other: Death, fever, influenza-like symptoms, tumor progression.

USE IN SPECIAL POPULATION

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 foetus.

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.

Pediatric use:

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

Pediatric 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 pediatric patients less than 5 years of age have not been established

Geriatric use: No overall differences in safety or effectiveness have been observed between geriatric and younger patients.

DRUG INTERACTIONS

There is no evidence of interaction of erythropoietin with other drugs.

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 IU/kg TIW for 3 to 4 weeks have been administered to adults without any direct toxic effects of erythropoietin itself. Therapy with erythropoietin can result in polycythemia if the hemoglobin is not carefully monitored and the dose appropriately adjusted. If the suggested target range is exceeded, erythropoietin may be temporarily withheld until the hemoglobin returns to the suggested target range; erythropoietin therapy may then be resumed using a lower dose. If polycythemia is of concern, phlebotomy may be indicated to decrease the hemoglobin.

STORAGE

Store at 2°C to 8°C. Protect from light. Do not freeze or shake.

SHELF LIFE

Please refer to the carton for shelf life. Do not use beyond expiration date stamped on the label and carton.

PRESENTATION

Vials / Pre-Filled Syringes of 2000 / 3000 / 4000 / 6000 / 10000 / 20000 / 40000 International Units
KEEP AWAY FROM THE REACH OF CHILDREN.

To report any safety-related events and product complaints with this product please write to :
For India :
PV.R&D@EMCURE.CO.IN
For Rest of the World :
SAFETY.ROW@EMCURE.CO.IN
Manufactured by :

Gennova Biopharmaceuticals Ltd.
Block 1, Plot No. P-1 & P-2, I.T.B.T. Park, Phase II,
MIDC, Hinjawadi, Pune - 411057, India.

Revised in September 2018
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For the use of Registered Medical Practitioner or Hospital or Laboratory only

Erythropoietin Injection I.P.

2000/3000/4000/6000/10000/20000/40000 IU/ml

VINTOR®-2000/3000/4000/6000 10000/20000/40000

For SC/IV Administration

WARNINGS: ERYTHROPOIESIS STIMULATING AGENTS (ESAs) INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE

Chronic Renal Failure (CRF):
- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a haemoglobin level of greater than 11 g/dL.
- No trial has identified a haemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.
- Use the lowest Recombinant Human Erythropoietin (r-Hu-EPO) dose sufficient to reduce the need for red blood cell (RBC) transfusions

Cancer:
- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in 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 cardio and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusion.
- Use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy.
- ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.
- Discontinue following the completion of a chemotherapy course.

Perisurgery:
r-Hu-EPO injection increased the rate of deep venous thromboses in patients not receiving prophylactic anticoagulation. Consider deep venous thrombosis prophylaxis.

COMPOSITION

VINTOR is formulated as a sterile clear solution for subcutaneous or intravenous administration.
Each Single Dose Vial/Pre-Filled Syringe of VINTOR 2000 / VINTOR 3000 / VINTOR 4000 / VINTOR 6000 / VINTOR 10000 / VINTOR 20000 Contains Erythropoietin Concentrated Solution I.P. 2000/ 3000/4000/6000/10000/20000 IU respectively, Excipients are Human Albumin I.P. - 2.5 mg, Sodium Citrate Dihydrate I.P. - 5.8 mg, Sodium Chloride I.P. - 5.8 mg and Citric Acid Monohydrate I.P. - 0.06 mg in Water for Injections I.P. q.s. to 1.0 ml.
This formulation contains no preservative.
Each Single Dose Vial / Pre-Filled Syringe of VINTOR 40000 contains Erythropoietin Concentrated Solution I.P. - 40000 IU Excipients are Human albumin I.P. - 2.5 mg, Monosodium Phosphate Monohydrate I.P. - 1.2 mg, Anhydrous Disodium Hydrogen Phosphate Ph. Eur. - 1.8 mg, Sodium Citrate Dihydrate I.P. - 0.7 mg, Sodium Chloride I.P. - 5.8 mg and Citric Acid Monohydrate I.P. - 6.8 mcg in Water for Injections I.P. q.s. to 1.0 ml.
This formulation contains no preservative.

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. r-Hu-EPO is a 165 amino acid erythropoiesis-stimulating glycoprotein manufactured by recombinant DNA technology and has the same biological effects as endogenous erythropoietin. It is formulated as a sterile, colorless, isotonic buffered solution for intravenous (IV) or subcutaneous (SC) administration in preservative-free single dose vials / pre-filled syringes (PFS).

CLINICAL PHARMACOLOGY

Mechanism of action

r-Hu-EPO stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. 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.

Pharmacodynamics

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. 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 IU/kg thrice weekly (TIW). A greater biologic response is not observed at doses exceeding 300 IU/kg TIW.

Pharmacokinetics

In adult and pediatric patients with CRF, the elimination half-life of plasma erythropoietin after intravenous administration ranges from 4 to 13 hours. The half-life is approximately 20% longer in CRF patients than that in healthy subjects. After subcutaneous administration, peak plasma levels are achieved within 5 to 24 hours. The half-life is similar between adult patients with serum creatinine level greater than 3 mg/dL and not on dialysis and those maintained on dialysis. The pharmacokinetic data indicate no apparent difference in erythropoietin half-life among adult patients above or below 65 years of age. The pharmacokinetic profile of erythropoietin in children and adolescents appears to be similar to that of adults. The pharmacokinetics of erythropoietin has not been studied in HIV-infected patients.Distribution volume is approximately 1.5 to 2 times higher in the preterm neonates than in the healthy adults, and clearance is approximately 3 times higher in the preterm neonates than in the healthy adults.

INDICATIONS AND USAGE

Treatment of anemia of chronic renal failure patients: Erythropoietin is indicated for the treatment of anemia associated with CRF, including patients on dialysis (ESRD) and patients not on dialysis.

VIN'S 21918

VINTOR-2000/3000/4000/6000 10000/20000/40000
Same Size Pack Insert Artwork (Front & Back)
Actual Size : L. 240 x H. 360 mm
Date : 23.02.2018 (Proof)
Date : 26.02.2018 (Proof)
Date : 07.03.2018 (Proof)
Date : 15.03.2018 (Proof)
Date : 22.03.2018 (Proof)
Date : 06.04.2018 (Proof)
Date : 10.04.2018 (Proof)
Date : 11.04.2018 (Proof)
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Date : 10.08.2018 (Proof)
Date : 23.08.2018 (Proof)
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Date : 03.09.2018 (Proof)
Date : 07.09.2018 (Proof)
Date : 21.09.2018 (Proof)
Fact. : Packaging (Mr. Shrikant Pandit)

FRONT

Generic Name Font & Font Size - Arial, Normal 21 pt
Brand Name Font & Font Size - Arial, Bold, 19 pt
Text Matter Font & Font Size - Myriad Pro Normal 9 pt

Treatment of anemia in zidovudine-treated HIV-infected patients: Erythropoietin is indicated for the treatment of anemia related to therapy with zidovudine when the endogenous serum erythropoietin level is ≤ 500 mIU/mL and when patients are receiving a dose of zidovudine ≤ 4200 mg/week.

Treatment of anemia in cancer patients on chemotherapy: 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 ≤13 g/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 pre-operatively.

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

Pretherapy iron evaluation: 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. Prior to and during erythropoietin therapy, the patient's iron stores, including transferrin saturation and serum ferritin, should be evaluated. Transferrin saturation should be at least 20%, and ferritin should be at least 100 ng/mL.

Patients with chronic kidney disease (CKD):

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 1 g/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 1 g/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 10 g/dL.
- If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of erythropoietin.
- The recommended starting dose for adult patients is 50 to 100 IU/kg 3 times weekly intravenously or subcutaneously. For pediatric patients, a starting dose of 50 IU/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 10 g/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 10 g/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 IU/kg 3 times weekly intravenously or subcutaneously.

Zidovudine-treated HIV-infected patients:

Starting dose:

For adult patients with serum erythropoietin levels ≤ 500 mIU/mL who are receiving a dose of zidovudine ≤ 4200 mg/week, the recommended starting dose of erythropoietin is 100 IU/kg as an IV or SC injection TIW for 8 weeks.

Maintenance dose:

- If hemoglobin does not increase after 8 weeks of therapy, increase erythropoietin dose by approximately 50 to 100 IU/kg at 4- to 8-week intervals until hemoglobin reaches a level needed to avoid RBC transfusions or 300 IU/kg dose is reached.
- If the hemoglobin exceeds 12 g/dL, the dose should be discontinued. Resume therapy at a dose 25% below the previous dose when hemoglobin declines to less than 11 g/dL.
- Discontinue erythropoietin if an increase in hemoglobin is not achieved at a dose of 300 IU/kg for 8 weeks.

Cancer patients on chemotherapy:

Initiate erythropoietin in patients on cancer chemotherapy only if the hemoglobin is less than 10 g/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 IU/kg subcutaneously 3 times per week until completion of a chemotherapy course or
- 40000 IU subcutaneously weekly until completion of a chemotherapy course.

Pediatric Patients (5 to 18 years):

- 600 IU/kg intravenously weekly until completion of a chemotherapy course.

Dose Reduction

Reduce dose by 25% if:

- Hemoglobin increases greater than 1 g/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 1 g/dL and remains below 10 g/dL, increase dose to:

- 300 IU/kg three times per week in adults or
- 60000 IU weekly in adults
- 900 IU/kg (maximum 60000 IU) 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 IU/kg per day subcutaneously for 14 days total: administered daily for 10 days before surgery, on the day of surgery, and for 4 days after surgery.
- 600 IU/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.

Preparation and administration of erythropoietin:

1. Erythropoietin may be given either as an IV or SC injection.
2. While the administration of erythropoietin is independent of the dialysis procedure, erythropoietin may be administered into the venous line at the end of the dialysis procedure to obviate the need for additional venous access.
3. Do not shake and/or freeze.
4. Protect from light.
5. Do not use any formulation exhibiting particulate matter or discoloration.
6. Do not dilute or administer in conjunction with other drug solutions.

CONTRAINDICATIONS

1. Uncontrolled hypertension.
2. Pure red cell aplasia (PRCA) that begins after treatment with erythropoietin protein drugs
3. Known hypersensitivity to mammalian cell-derived products.
4. Known hypersensitivity to Human Albumin.

WARNINGS AND PRECAUTIONS

Increased mortality, serious cardiovascular events, thromboembolic events, and stroke:

- In controlled clinical trials of patients with CKD comparing higher hemoglobin targets (13 - 14 g/dL) to lower targets (9 - 11.3 g/dL), erythropoietin and other ESAs increased the risk of death, myocardial infarction, stroke, congestive heart failure, thrombosis of hemodialysis vascular access, and other thromboembolic events in the higher target groups.
- Using ESAs to target a hemoglobin level of greater than 11 g/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. Patients with CKD and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular reactions and mortality than other patients. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may contribute to these risks.
- In controlled clinical trials of patients with cancer, ESAs increased the risks for death and serious adverse cardiovascular reactions. These adverse reactions included myocardial infarction and stroke.
- In controlled clinical trials, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and the risk of deep venous thrombosis (DVT) in patients undergoing orthopedic procedures.

Increased mortality and/or increased risk of tumor progression or recurrence: Erythropoiesis-stimulating agents resulted in decreased locoregional control/progression-free survival and/or overall survival. Published data reported that these findings were observed in studies of patients with advanced head and neck cancer receiving radiation therapy, in patients receiving chemotherapy for metastatic breast cancer or lymphoid malignancy, and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy.

Pure red cell aplasia: Cases of pure red cell aplasia (PRCA) and of severe anemia, with or without other cytopenias, associated with neutralizing antibodies to erythropoietin have been reported in patients treated with erythropoietin from some sources. This has been reported predominantly in patients with CRF receiving ESAs by subcutaneous administration. PRCA has also been reported in patients receiving ESAs while undergoing treatment for hepatitis C with interferon and ribavirin. Any patient who develops a sudden loss of response to erythropoietin, accompanied by severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin. If anti-erythropoietin antibody associated anemia is suspected, withhold erythropoietin and other ESAs. Erythropoietin should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other ESAs as antibodies may cross-react.

Human Albumin: Erythropoietin formulation contains albumin, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

Hypertension: Patients with uncontrolled hypertension should not be treated with erythropoietin; blood pressure should be controlled adequately before initiation of therapy. Although there does not appear to be any direct pressor effects of erythropoietin, blood pressure may rise during erythropoietin 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. Special care should be taken to closely monitor and aggressively control blood pressure in patients treated with erythropoietin. If blood pressure is difficult to control by initiation of appropriate measures, the hemoglobin may be reduced by decreasing or withholding the dose of erythropoietin. It is recommended that the dose of erythropoietin be decreased if the hemoglobin increase exceeds 1 g/dL in any 2-week period. In CRF patients on hemodialysis with clinically evident ischemic heart disease or congestive heart failure, the dose of erythropoietin should be carefully adjusted to achieve and maintain hemoglobin levels between 10-12 g/dL

Seizures: Seizures have been reported with erythropoietin. Given the potential for an increased risk of seizures during the first 90 days of therapy, blood pressure and the presence of premonitory