

(Recombinant human erythropoietin)
Shanpoetin®

Composition

Each Pre-filled syringes of *Shanpoetin* contains 2000 IU or 4000 IU of recombinant erythropoietin in 0.5 or 1 ml respectively of isotonic sodium chloride/sodium citrate buffered solution with human serum albumin.

Active ingredient

Recombinant erythropoietin.

Form

Shanpoetin is supplied as liquid in Pre-filled syringes.

Source

Shanpoetin is derived from genetically modified Chinese hamster ovary (CHO) cells.

Properties and mechanism of action

Erythropoietin (EPO) is a sialoglycoprotein hormone, which is the primary regulator of red blood cell formation in mammals. Recombinant human erythropoietin (r-HuEPO) is a purified glycoprotein, produced from mammalian cells into which the gene coding for human erythropoietin has been inserted and has a molecular mass of about 30 000 daltons. The carbohydrate moiety with three N-linked and one O-linked carbohydrate groups corresponds to a mass fraction of approximately 40%. Erythropoietin acts on receptors in the progenitor cells and stimulates erythropoiesis.

Pharmacokinetics

Measurement of the r-HuEPO following multiple dose intravenous administration revealed a half-life of approximately 4 hours in normal healthy volunteers and a more prolonged half-life in renal failure patients, approximately 5 hours.

Subcutaneous route

Following subcutaneous injection, serum levels are much lower than those achieved following intravenous injection, the levels increase slowly and reach a peak between 12 and 18 hours post-dose. The peak is always well below that achieved using the intravenous route. There is no accumulation. The half-life is difficult to evaluate for the subcutaneous route and is estimated to be about 24 hours. The bioavailability of subcutaneous injectable erythropoietin is much lower than that of the intravenously administered erythropoietin i.e. approximately 20%.

Indications

Erythropoietin is indicated in the management of

- Anemia of chronic renal failure patients.
- Anemia in Zidovudine- treated HIV infected patients
- Anemia in cancer patients on chemotherapy
- To increase the yield in autologous Blood transfusion.
- To increase the red cell production and hasten erythroid recovery for patients undergoing elective surgery.

Dosage

Anemia of chronic renal failure: Erythropoietin is administered so as to maintain hemoglobin concentration between 11 to 12 g/dl and haematocrit of 33 –36 % in adults.

Starting dose is usually 50 to 100 IU/Kg thrice a week by IV or SC route thrice weekly. The dose is increased if the hemoglobin does not increase by at least 1 g/dl/month or the haematocrit increase is <2 % over 2-4 week period. An increase in haematocrit is usually observed between 2 to 10 weeks with over 50% patients responding after 2 weeks of therapy. In a phase III study over 90% patients responded following 12 weeks of erythropoietin therapy.

Maintenance dose The dose reduction is at the discretion of the physician and should be individualized for each patient. Whenever the hemoglobin concentration exceeds 12 g /dl or haematocrit increases to ≥40% the dose is titrated or therapy is stopped, dose is reduced by either omitting or reducing the amount per dose.¹

Zidovudine-treated HIV-infected Patients: The endogenous serum erythropoietin has to be determined (prior to administration). Evidence suggests that patients receiving zidovudine with endogenous serum erythropoietin levels > 500 mUnits/mL are unlikely to respond to therapy.

Starting Dose: For adult patients, the recommended starting dose is 100 Units/kg as an IV or SC injection TIW for 8 weeks. During the dose adjustment phase of therapy, the haematocrit should be monitored weekly. If the response is not satisfactory the dose can be increased by 50 to 100 Units/kg TIW. Response should be evaluated every 4 to 8 weeks thereafter and the dose adjusted accordingly by 50 to 100 Units/kg increments TIW. If patients have not responded satisfactorily to a dose of 300 Units/kg TIW, it is unlikely that they will respond to higher doses of erythropoietin.

Maintenance Dose: The dose is titrated to maintain the haematocrit between 33-36% if the haematocrit increases over 40% then the dose is withheld until the levels falls below 36%. The dose should be reduced by 25% when treatment is resumed and then titrated to maintain the desired haematocrit.

Cancer Patients on Chemotherapy²

Starting Dose: The recommended starting dose of erythropoietin for adults is 150 Units/kg SC TIW or 40,000 IU /week.

Dose Adjustment: If the response is not satisfactory the dose can be increased up to 300 Units/kg TIW. If patients have not responded satisfactorily to dose of 300 Units/kg TIW, it is unlikely that they will respond to higher doses. The hemoglobin levels need to be maintained at 12 gm/dl and the haematocrit at 36%. If the hemoglobin levels increase < 1 gm.dl after a dose of 300 IU/Kg no response is expected at higher doses. If the hemoglobin levels increase > 2gm/dl per month or the haematocrit increase > 4% over a two week period then the dose is to be reduced by 25%. The therapy is discontinued if hemoglobin increases more than 14 gm/dl and is withheld until hemoglobin falls below 12 gm/dl and then the dose is reduced by 25% and continued.

Administration

a) Administer as intravenous injection over 1-2 minutes. In patients on dialysis, the injection should follow the dialysis procedure. Slow injection over 5 minutes may be beneficial to those who experience flu-like symptoms.

b) Do not administer by intravenous infusion or in conjunction with other drug solutions.

c) For the subcutaneous route a maximum of 1 mL at one injection site should generally not be exceeded. In the case of larger volumes, more than one site should be chosen for the injection.

Side effects

General: headache, dizziness, fever, malaise, arthralgia and occasionally hyperkalemia

Allergic reactions: Rarely skin rashes and urticaria have been reported.

CVS: Hypertension most common side effect rarely palpitations.

Hepatic: Elevation of ALT and AST (rare)

Gastrointestinal: nausea, vomiting, anorexia and diarrhea may occur occasionally.

Contraindications

Erythropoietin is contraindicated in patients with:

1. Uncontrolled hypertension
2. Known hypersensitivity to mammalian cell-derived products
3. Known hypersensitivity to Albumin (Human)
4. A history of hypersensitivity to *Shanpoetin* or any component of the preparation.

Precautions

Erythropoietin should be used with caution in those patients with controlled hypertension, ischaemic vascular disease, history of seizures, or suspected allergy to the product.

Preclinical experience

Acute and Sub acute toxicity studies were carried out in rats and Mice. The maximum dose of *Shanpoetin* administered was 10 times the highest human therapeutic dose. In acute toxicity studies animals were administered single intravenous dose of *Shanpoetin* and observed for 14 days. In subacute studies animals were administered *Shanpoetin* once daily for 28 days and observed for 14 days. *Shanpoetin* has been shown to be safe without causing any Biochemical, hematological abnormalities and histopathological changes.

Human clinical trials¹

Phase III clinical trial using (*Shanpoetin*) was carried out at six centers across the country. One hundred and one patients were recruited. Significant rise in Hematocrit was observed in 90.2 % of the patients. Overall 80.5% of patients showed a ≥ 6 % Increases of haematocrit from the baseline.

1. Total RBC count increased from 2.6 ± 0.6/cmm to 3.3±0.6/cmm
2. Hemoglobin increased from 7.0 ± 1.4gm/dl to 9.8± 1.7gm/dl
3. Haematocrit increased from 21.7 ± 3.9 % to 30.4 ± 5.1%

There was a 35% reduction in serum ferritin levels in patients with Iron overload. No evidence for development of antibodies to erythropoietin was observed. The most common side effects reported with *Shanpoetin* were Hypertension (5.9%), Fever and flu like illness (3.9%), Vomiting (2.9%), Diarrhea (0.9 %), Anorexia (0.9 %), Dyspnoea (0.9 %), Cough (0.9%), Myalgia (0.9%). These side effects were transient and not severe.

Drug interactions

There are no known clinically significant interactions, but the effect of r-HuEPO may be potentiated by the simultaneous therapeutic administration of a haematinic agent such as ferrous sulphate when a deficiency state exists.

Pharmaceutical Details Of Shanpoetin

Presentation: *Shanpoetin* is available as:

Pre-filled syringes containing

1. 2000 IU/0.5 mL
2. 4000 IU/1.0 mL

Storage:

Shanpoetin should be stored at +2 to +8°C.

Shanpoetin must not be used after the expiry date given on the pack and Syringe.

Keep out of reach of children.

Legal Category

Schedule H

References

1. Data on file. Shantha Biotechnics. Pvt. Ltd.
2. NEJM 1990; 322: 1488-1493
3. J Clin Oncol 2002; 20:4083-4107.

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