

Epotex® Benta

Recombinant Human Erythropoietin Alpha (rHuEPO Alpha)

FORMS AND PRESENTATION

Epotex® 2000 Benta: Injectable 1 mL. Box of 1 prefilled syringe.
Epotex® 4000 Benta: Injectable 1 mL. Box of 1 or 6 prefilled syringes.

COMPOSITION

Epotex® 2000: Each 1 mL contains Recombinant Human Erythropoietin Alpha 2000 IU.
Epotex® 4000: Each 1 mL contains Recombinant Human Erythropoietin Alpha 4000 IU.
Excipients: human serum albumin, sodium citrate, sodium chloride, citric acid, water for injection.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: anti-anemic, ATC code: B03XA01.

Mechanism of action

Erythropoietin (EPO) is a glycoprotein hormone produced primarily by the kidney in response to hypoxia that regulates red blood cell production (RBC), acting on erythroid precursors. EPO binds to receptors, triggers cell signaling, prevents cell death, and promotes cell growth with molecular weight: 32,000-40,000 daltons. EPO primarily stimulates RBC and may be found on some other cells.

Pharmacokinetic properties

Intravenously (IV) administered rHuEPO Alpha is eliminated via first-order kinetics with a half-life of 4-13 hours in adult and pediatric chronic renal failure (CRF) patients. Plasma EPO remains detectable for 24 hours within therapeutic doses. Subcutaneous (SC) administration leads to peak serum levels in 5-24 hours, with a gradual decline. Pediatric pharmacokinetics are similar to that of adults. Limited data available for neonates.

INDICATIONS

Epotex® Benta is indicated:

- for the treatment of symptomatic anaemia associated with CRF;
 - in adults and paediatrics aged 1 to 18 years on haemodialysis and adult patients on peritoneal dialysis.
 - in adults with renal insufficiency not yet undergoing dialysis for the treatment of severe anaemia of renal origin accompanied by clinical symptoms in patients.
 - in adults receiving solid tumours, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy) for the treatment of anaemia and reduction of transfusion requirements.
 - in adults in a predonation programme to increase the yield of autologous blood. Treatment should only be given to patients with moderate anaemia (haemoglobin (Hb) concentration range 10-13 g/dL [6.2 to 8.1 mmol/L], no iron deficiency) if blood saving procedures are not available or insufficient when the scheduled major elective surgery requires a large volume of blood (4 or more units of blood for females or 5 or more units for males).
 - for non-iron deficient adults prior to major elective orthopaedic surgery having a high perceived risk for transfusion complications and/or exposure to allogeneic blood transfusions. Use should be restricted to patients with moderate anaemia (e.g. Hb concentration range 10-13 g/dL) who do not have an autologous predonation programme available and with expected moderate blood loss (900 to 1,800 mL).
 - for the treatment of symptomatic anaemia (Hb concentration of ≤ 10 g/dL) in adults with low- or intermediate-1-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin (<200 mU/mL).
- ## CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients listed.
 - Patients who develop pure red cell aplasia (PRCA) following treatment with any erythropoietin.

Uncontrolled hypertension.

- All contraindications associated with autologous blood predonation programmes should be respected in patients being supplemented with rHuEPO.

The use of rHuEPO Alpha in patients scheduled for major elective orthopaedic surgery and not participating in an autologous blood predonation programme is contraindicated in patients with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including patients with recent myocardial infarction or cerebral vascular accident.

-Surgery patients who for any reason cannot receive adequate antithrombotic prophylaxis.

PRECAUTIONS

Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have occurred also during rHuEPO Alpha treatment in patients with previously normal or low blood pressure. Particular attention should be paid to sudden stabbing migraine-like headaches as a possible warning signal.

-rHuEPO Alpha should be used with caution in patients with epilepsy, history of seizures, or medical conditions associated with a predisposition to seizure activity such as CNS infection and brain metastases.

-rHuEPO Alpha should be used with caution in patients with chronic liver failure.

-An increased incidence of thrombotic vascular events (TVEs) has been observed in patients receiving erythropoietin-stimulating agents (ESAs). These include venous and arterial thromboses and embolism (including some with fatal outcomes), obesity and prior history of TVEs such as deep venous thrombosis, pulmonary emboli, retinal thrombosis, and myocardial infarction. Additionally, cerebrovascular accidents (including cerebral infarction, cerebral haemorrhage and transient ischaemic attacks) have been reported.

-All other causes of anaemia (iron, folate or Vitamin B₁₂ deficiency, aluminium intoxication, infection or inflammation, blood loss, haemolysis and bone marrow fibrosis of any origin) should be evaluated and treated prior to initiating therapy with rHuEPO Alpha, and when deciding to increase the dose. In most cases, the ferritin values in the serum fall simultaneously with the rise in packed cell volume.

-Very rarely, development or exacerbation of porphyria has been observed in rHuEPO Alpha treated patients. rHuEPO Alpha should be used with caution in patients with porphyria.

-Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with epoetin treatment. At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions.

-**Chronic renal failure:** rHuEPO Alpha is not approved in the management of anaemia associated with hepatitis C.

-**Red cell aplasia:** patients being treated with rHuEPO Alpha should have Hb levels measured on a regular basis until a stable level is achieved, and periodically thereafter.

Shunt thromboses have occurred in haemodialysis patients, especially in those who have a tendency to hypotension or whose arteriovenous fistulae exhibit complications (e.g. stenosis, aneurysms, etc.). Serum electrolytes should be monitored in chronic renal failure patients. Occlusion of the dialysis system is possible if heparinisation is not optimum.

-Cancer patients being treated with rHuEPO Alpha should have Hb levels measured on a regular basis until a stable level is achieved, and periodically thereafter. The role of ESAs on tumour progression or reduced progression-free survival cannot be excluded.

In cancer patients receiving chemotherapy, the 2-to-3-week delay between ESA administration and the appearance of EPO-induced red cells should be taken into account when assessing if rHuEPO Alpha therapy is appropriate (patient at risk of being transfused).

-Surgery patients in autologous predonation programmes: All special warnings and special precautions should be respected.

-Patients scheduled for major elective orthopaedic surgery: Good blood management practices should always be used in the perioperative setting. And these patients should receive adequate antithrombotic prophylaxis. Therefore, rHuEPO Alpha should not be used in patients with a baseline Hb >13 g/dL.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

PREGNANCY AND LACTATION

Limited data are available in pregnant women; use if benefits outweigh risks. Unknown if EPO excreted in breast milk; caution advised for nursing women.

DRUG INTERACTIONS

Treatment with rHuEPO Alpha does not affect the metabolism of other drugs.

ADVERSE EFFECTS

The following adverse reactions from clinical investigations are listed below:

Very common ($\geq 1/10$): pyrexia; diarrhoea, nausea, vomiting.

Common ($\geq 1/100$ to $< 1/10$): arthralgia, bone pain, myalgia, pain in extremity; chills, influenza like illness, injection site reaction, oedema peripheric, arthralgia, bone pain, myalgia, pain in extremity; rash; cough; headache; hypertension, venous and arterial thromboses.

Uncommon ($\geq 1/1,000$ to $< 1/100$): urticaria; respiratory tract congestion; convulsion; hypersensitivity; hyperkalaemia. **Rare ($\geq 1/10,000$ to $< 1/1,000$):** pure red cell aplasia, thrombocythemia; anaphylactic reaction; porphyria acute.

Very rare ($< 1/10,000$): cannot be available data; drug ineffective; angioneurotic oedema; hyperviscous crisis.

DOSEAGE AND ADMINISTRATION

Method of administration

Precautions to be taken before handling or administering the medicinal product. As with any other injectable product, check that there are no particles in the solution or change in colour.

-IV administration: administer over at least one to five minutes, depending on the total dose. In haemodialysed patients, a bolus injection may be given during the dialysis session through a suitable venous port in the dialysis line. Alternatively, the injection can be given at the end of the dialysis session via the fistula needle tubing, followed by 10 mL of isotonic saline solution to ensure the tubing and ensure satisfactory injection of product into the circulation.

A slower administration is preferable in patients who react to the treatment with "flu-like" symptoms. Do not administer Epotex® Benta by IV infusion or in conjunction with other drug solutions.

-SC administration: a maximum volume of 1 mL at one injection site should generally not be exceeded. In case of larger volume, divide the dose into one site. The injection should be given in the limbs or the anterior abdominal wall. In those situations, in which the physician determines that a patient or caregiver can safely and effectively administer Epotex® Benta subcutaneously themselves, instruction as to the proper dosage and administration should be provided.

Treatment of symptomatic anaemia in adult and pediatric chronic renal failure patients

Anaemia symptoms and sequelae may vary with age, gender, and co-morbid medical conditions; a physician's evaluation of the individual patient's clinical course and condition is necessary. The recommended desired haemoglobin concentration range is 10-12 g/dL (6.2 to 7.5 mmol/L). Epotex® Benta should be administered in order to increase Hb to Hb ≥ 12 g/dL (7.5 mmol/L). A rise in haemoglobin of ≥ 2 g/dL (1.25 mmol/L) over a 4 weeks period should be avoided. If it occurs, appropriate dose adjustment should be made as provided. Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired Hb concentration range may be observed. Hb variability should be addressed through dose management, with consideration for the haemoglobin concentration range mentioned above. In paediatric patients on haemodialysis where IV access is readily available, administration by the IV route is preferable and the recommended haemoglobin concentration range is 9.5-11 g/dL (5.9 to 6.8 mmol/L). A sustained haemoglobin level of ≥ 12 g/dL (7.5 mmol/L) should be avoided. If the Hb is rising by more than 2 g/dL (1.25 mmol/L) per month, or if the sustained Hb exceeds 12 g/dL (7.5 mmol/L) reduce the Epotex® Benta dose by 25%. If the Hb increases by 13 g/dL (8.1 mmol/L), discontinue therapy until it falls below 12 g/dL (7.5 mmol/L) and then reinstitute Epotex® Benta therapy at a dose 25% below the previous dose. Patients should be monitored closely to ensure that the lowest effective dose of Epotex® Benta is used to provide adequate control of anaemia and of the symptoms of anaemia whilst maintaining a Hb concentration ≤ 12 g/dL (7.5 mmol/L).

Adult and paediatric haemodialysis patients

In patients on haemodialysis where intravenous access is readily available, administration by the IV route is preferable. The treatment is divided into two stages:

-**Correction phase:** 50 IU/kg, 3 times per week. If necessary, increase or decrease the dose by 25 IU/kg (3 times per week) until the desired Hb concentration range is 10-12 g/dL (6.2 to 7.5 mmol/L) for adults and 9.5-11 g/dL (5.9 to 6.8 mmol/L) for paediatric is achieved (this should be done in steps of at least four weeks).

-**Maintenance phase:** the recommended total weekly dose is 75-300 IU/kg. Dosage adjustment in order to maintain Hb values within the desired level: Hb range 10-12 g/dL (6.2 to 7.5 mmol/L) for adults and 9.5-11 g/dL (5.9 to 6.8 mmol/L) for paediatric patients. At < 6 g/dL (3.75 mmol/L) or > 13 g/dL (8.1 mmol/L) may require higher maintenance doses than patients whose initial anaemia is less severe (< 8 g/dL or > 13 g/dL). Paediatric patients with very low initial Hb (< 6.8 g/dL or < 4.25 mmol/L) may require higher maintenance doses than patients whose initial Hb is higher (> 6.8 g/dL or > 4.25 mmol/L).

Adult patients with renal insufficiency not yet undergoing dialysis

Where IV access is not readily available Epotex® Benta may be administered subcutaneously.

-**Correction phase:** starting dose of 50 IU/kg, 3 times per week, followed, if necessary, by a dosage increase with 25 IU/kg increments (3 times per week) until the desired goal is achieved (this should be done in steps of at least four weeks).

-**Maintenance phase:** during the maintenance phase, Epotex® Benta can be administered either 3 times per week, and in the case of subcutaneous administration, once weekly or once every 2 weeks. Dosage adjustment in order to maintain Hb values at the desired level: Hb range 10-12 g/dL (6.2 to 7.5 mmol/L). Extending dose intervals may require an increase in dose. The maximum dosage should not exceed 150 IU/kg 3 times per week.

Adult peritoneal dialysis patients

Where IV access is not readily available Epotex® Benta may be administered subcutaneously.

-**Correction phase:** starting dose is 50 IU/kg, 2 times per week.

-**Maintenance phase:** the recommended maintenance dose is between 25 IU/kg and 50 IU/kg, 2 times per week in 2 equal injections. Dosage adjustment in order to maintain Hb values at the desired level is 10-12 g/dL (6.2 to 7.5 mmol/L).

Adult patients with chemotherapy-induced anaemia

Anaemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary. Epotex® Benta should be administered to patients with anaemia (e.g. Hb concentration ≤ 10 g/dL (6.2 mmol/L)). The initial dose is 150 IU/kg subcutaneously, 3 times per week. Alternatively, Epotex® Benta can be administered at an initial dose of 450 IU/kg subcutaneously once weekly. Due to intra-patient variability, occasional individual Hb concentrations for a patient above and below the desired Hb concentration range may be observed. Hb variability should be addressed through dose management, with consideration for the desired haemoglobin concentration range 10-12 g/dL (6.2 to 7.5 mmol/L). A sustained Hb concentration of > 12 g/dL (7.5 mmol/L) should be avoided. Patients should be monitored closely to ensure that the lowest approved dose of ESA is used to provide adequate control of the symptoms of anaemia. Epotex® Benta therapy should continue until one month after the end of chemotherapy.

Adult surgery patients in an autologous predonation programme

Mildly anaemic patients (haematocrit of 33 to 39%) requiring predeposit of 24 units of blood should be treated with Epotex® Benta 600 IU/kg intravenously, 2 times per week for 3 weeks prior to surgery. Epotex® Benta should be administered after the completion of the blood donation procedure.

Adult patients scheduled for major elective orthopaedic surgery

The recommended dose is 600 IU/kg of Epotex® Benta administered subcutaneously weekly for three weeks (days -21, -14 and -7) prior to surgery and on the day of surgery. In cases where there is a medical need to shorten the lead time before surgery to less than three weeks, Epotex® Benta 300 IU/kg should be administered subcutaneously daily for 10 consecutive days prior to surgery, on the day of surgery and for four days immediately thereafter. If the Hb level reaches 15 g/dL, or higher, during the preoperative period, administration of Epotex® Benta should be stopped and further dosages should not be administered.

Adult patients with low- or intermediate-1-risk MDS

Epotex® Benta should be administered to patients with symptomatic anaemia (e.g. Hb concentration ≤ 10 g/dL (6.2 mmol/L)). The recommended starting dose is 450 IU/kg (maximum total dose is 40,000 IU) of Epotex® Benta administered subcutaneously once every week, with not less than 5 days between doses. Appropriate dose adjustments should be made to maintain Hb concentrations within the target range of 10-12 g/dL (6.2 to 7.5 mmol/L). It is recommended that initial erythroid response be assessed 8 to 12 weeks following initiation of treatment. Dose increases and decreases should be done one dosing step at a time. A Hb concentration of > 12 g/dL (7.5 mmol/L) should be avoided.

Dose increase: Dose should not be increased over the maximum of 1050 IU/kg (total dose 80,000 IU) per week. If the patient loses response or Hb concentration drops by ≥ 1 g/dL upon dose reduction the dose should be increased by one dosing step. A minimum of 4 weeks should elapse between dose increases.

Dose hold and decrease: rHuEPO Alpha should be withheld when the Hb concentration exceeds 12 g/dL (7.5 mmol/L). Once the Hb level is ≤ 11 g/dL, the dose can be restarted on the same dosing step or one dosing step down based on physician judgement. Decreasing the dose by one dosing step should be considered if there is a rapid increase in Hb (> 2 g/dL over 4 weeks).

OVERDOSAGE

The therapeutic margin of epoetin alfa is very wide. Overdosage of epoetin alfa may produce effects that are extensions of the pharmacological effects of the hormone. Phlebotomy may be performed if excessively high Hb levels occur. Additional supportive care should be provided as necessary.

STORAGE CONDITIONS

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

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Marketing Authorization Holder & Manufacturer

Benta S.A.L. Lebanon

