Epotex® Benta

Recombinant Human Erythropoietin Alpha (rHuEPO Alpha)

FORMS AND PRESENTATION
Epotex® 2000 Benta: Injectable 1 mL.
Epotex® 4000 Benta: Injectable 1 mL.

COMPOSITION
Epotex® 2000 Benta: Each 1 mL contains Recombinant Human Erythropoietin Alpha 2000 IU.
Excipients: Human serum albumin, sodium citrate, sodium chloride, citric acid, water for injection.
Epotex® 4000 Benta: 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
Therapeutic class: Antianemic preperations.
ATC code: B03XA01.
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. rHuEPO Alpha, 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.
In vivo Pharmacodynamic Study was done on rHuEPO Alpha using normocythemic mice. Subcutaneous administration of rHuEPO Alpha in normocythemic mice induces reticulocyte production with single dosing of 0.5 ml of 10, 20, 40 IU / animal results in a dose dependent increase in reticulocyte count in 96 hours after the rHuEPO Alpha injection.
Pharmacokinetic Properties
Intravenously administered rHuEPO Alpha 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 chronic renal failure (CRF). Within the therapeutic dose range, detectable levels of plasma Erythropoietin are maintained for at least 24 hours. After SC administration of rHuEPO Alpha 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.
Preclinical Safety Data
Acute toxicity studies were conducted and the results suggested that the rHuEPO Alpha is toxicologically safe at the doses as high as 20 times more than the recommended human dose (150 IU/kg).
In subacute toxicity studies (with and without recovery) in two species with two routes of administration all the animals have shown normal hematology, biochemistry and histopathology of organs suggesting that rHuEPO Alpha is toxicologically safe at the doses as high as 20 times more than the recommended human dose (150 IU/kg).
rHuEPO Alpha was also evaluated for local irritation by conducting primary irritation test in rabbits (Draize test). The test drug was well tolerated and did not reveal any local intolerance or allergenicity potential.

INDICATIONS
-Treatment of symptomatic anemia associated with CRF in adult and pediatric patients:
• Treatment of anemia associated with CRF in pediatric and adult patients on hemodialysis and adult patients on peritoneal dialysis.
• Treatment of severe anemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing dialysis.
-Treatment of anemia and reduction of transfusion requirements in adult patients receiving chemotherapy for solid tumors, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status (e.g. cardiovascular status, pre-existing anemia at the start of chemotherapy).
- Treatment of anemia related to therapy with zidovudine in HIV-infected patients. 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.
- Epotex® Benta can be used to increase the yield of autologous blood from patients in a predonation program. Its use in this indication must be balanced against the reported risk of thromboembolic events. Treatment should only be given to patients with moderate anemia (Hb 10-13 g/dl [6.2-8.1 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).
- Epotex® Benta can be used to reduce exposure to allogeneic blood transfusions in adult non-iron deficient patients prior to major elective orthopedic surgery, having a high perceived risk for transfusion complications. Use should be restricted to patients with moderate anemia (e.g. Hb 10-13 g/dl) who do not have an autologous predonation program available and with expected moderate blood loss (900 to 1800 ml).

CONTRAINDICATIONS
rHuEPO Alpha is contraindicated in patients with:
- Uncontrolled hypertension.
- Known hypersensitivity to mammalian cell-derived products.
- Known hypersensitivity to Albumin (Human).

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 rHuEPO Alpha therapy; no serious allergic or anaphylactic reactions were reported.
The safety and efficacy of rHuEPO Alpha therapy have not been established in patients with a known history of a seizure disorder or underlying hematologic disease (e.g., sickle cell Anemia, myelodysplastic syndromes, or hypercoagulable disorders).
Seizures have occurred in patients with CRF participating in rHuEPO Alpha clinical trials. It is recommended that the dose of rHuEPO Alpha be decreased if the hematocrit increase exceeds 4 points in any 2-week period.
- Hematology: exacerbation of porphyria has been observed rarely in patients with CRF treated with rHuEPO Alpha, hence 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 (i.e., thalassemia, refractory anemia, or other myelodysplastic disorders); vitamin deficiencies (folic acid or vitamin B12); hemolysis; aluminum intoxication; osteitis fibrosa cystica.
- Iron Evaluation: prior to and during rHuEPO Alpha therapy, the patient's iron status, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Transferrin saturation should be at least 20% and ferritin should be at least 100 ng/mL. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels, which will adequately support erythropoiesis stimulated by Erythropoietin.
- 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)].
During hemodialysis, patients treated with rHuEPO Alpha may require increased anticoagulation with heparin to prevent clotting of the artificial kidney.
- Hypertension: patients with uncontrolled hypertension should not be treated with rHuEPO Alpha; 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 rHuEPO Alpha.

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

DRUG INTERACTIONS
No evidence of interaction of rHuEPO Alpha with other drugs was observed in the course of clinical trials.

ADVERSE EFFECTS
rHuEPO Alpha is generally well tolerated. The adverse events reported are frequent sequelae of disease and are not necessarily attributable to rHuEPO Alpha therapy. The events reported in greater than 5% of patients treated with rHuEPO Alpha 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 rHuEPO Alpha were rare, mild, and transient, and included injection site stinging in dialysis patients and flu-like symptoms such as arthralgias and myalgias.

DOSAGE AND ADMINISTRATION
Method of administration:
As with any other injectable product, check that there are no particles in the solution or change in colour.
- Intravenous injection: over at least one to five minutes, depending on the total dose. In hemodialysed 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 to rinse the tubing and ensure satisfactory injection of the product into the circulation.
A slower injection is preferable in patients who react to the treatment with "flu-like" symptoms.
Do not administer by intravenous infusion or mixed with other drugs.
- Subcutaneous injection: a maximum volume of 1 ml at one injection site should generally not be exceeded. In case of larger volumes, more than one site should be chosen for the injection.
The injections are 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, instruction as to the proper dosage and administration should be provided.
Treatment of symptomatic anemia in adult and pediatric CRF patients:
In patients with CRF where intravenous access is routinely available (hemodialysis patients) administration by the intravenous route is preferable. Where intravenous access is not readily available (patients not yet undergoing dialysis and peritoneal dialysis patients) Epotex® Benta may be administered subcutaneously.
Anemia 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.
Epotex® Benta should be administered in order to increase hemoglobin to not greater than 12 g/dl (7.5 mmol/l). A rise in hemoglobin of greater than 2g/dl (1.25 mmol/l) over a four week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.
Due to intra-patient variability, occasional individual hemoglobin values for a patient above and below the desired hemoglobin level may be observed. Hemoglobin variability should be addressed through dose management, with consideration for the hemoglobin target range of 10g/dl (6.2 mmol/l) to 12g/dl (7.5mmol/l). In pediatric patients the recommended target hemoglobin range is between 9.5 and 11 g/dl (5.9-6.8 mmol/l).
A sustained hemoglobin level of greater than 12g/dl (7.5mmol/l) should be avoided. If the hemoglobin is rising by more than 2 g/dl (1.25 mmol/l) per month, or if the sustained hemoglobin exceeds 12g/dl (7.5mmol/l) reduce the rHuEPO Alpha dose by 25%. If the hemoglobin exceeds 13 g/dl (8.1 mmol/l), discontinue therapy until it falls below 12 g/dl (7.5 mmol/l) and then reinstitute rHuEPO Alpha therapy at a dose 25% below the previous dose.
Patients should be monitored closely to ensure that the lowest approved dose of Epotex® Benta is used to provide adequate control of anemia and of the symptoms of anemia.
Iron status should be evaluated prior to and during treatment and iron supplementation administered if necessary. In addition, other causes of anemia, such as B_{12} or folate deficiency, should be excluded before instituting therapy with rHuEPO Alpha. Non response to rHuEPO Alpha therapy should prompt a search for causative factors. These include: iron, folate, or Vitamin B_{12} deficiency; aluminium intoxication; intercurrent infections; inflammatory or traumatic episodes; occult blood loss; hemolysis; and bone marrow fibrosis of any origin.
Adult hemodialysis patients:
In patients on hemodialysis where intravenous access is readily available, administration by the intravenous route is preferable.
The treatment is divided into two stages:
- Correction phase: 50 IU/kg, 3 times per week.
When a dose adjustment is necessary, this should be done in steps of at least four weeks. At each step, the increase or reduction in dose should be of 25 IU/kg, 3 times per week.
- Maintenance phase: dosage adjustment in order to maintain hemoglobin values at the desired level: Hb between 10 and 12 g/dl (6.2 - 7.5 mmol/l). The recommended total weekly dose is between 75 and 300 IU/kg. The clinical data available suggest that those patients whose initial hemoglobin is very low (<6 g/dl or <3.75 mmol/l) may require higher maintenance doses than those whose initial anemia is less severe (>8 g/dl or>5 mmol/l).
Pediatric hemodialysis patients:
The treatment is divided into two stages:
- Correction phase: 50 IU/kg, 3 times per week by the intravenous route. When a dose adjustment is necessary, this should be done in steps of 25 IU/kg, 3 times per week at intervals of at least 4 weeks until the desired goal is achieved.
- Maintenance phase: dosage adjustment in order to maintain hemoglobin values at the desired level: Hb between 9.5 and 11 g/dl (5.9 - 6.8 mmol/l).
Generally, children under 30 kg require higher maintenance doses than children over 30 kg and adults. For example, the following maintenance doses were observed in clinical trials after 6 months of treatment.

Dose (IU/kg given 3 times per week)		
Weight (kg)	Median	Usual maintenance dose
< 10	100	75-150
10-30	75	60-150
> 30	33	30-100

The clinical data available suggest that those patients whose initial hemoglobin is very low (<6.8 g/dl or <4.25 mmol/l) may require higher maintenance doses than those whose initial hemoglobin is higher (>6.8 g/dl or>4.25 mmol/l).
Adult patients with renal insufficiency not yet undergoing dialysis:
Where intravenous access is not readily available Epotex® Benta may be administered subcutaneously. The treatment is divided into two stages:
- 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: dosage adjustment in order to maintain hemoglobin values at the desired level: Hb between 10 and 12 g/dl (6.2 - 7.5 mmol/l) (maintenance dose between 17 and 33 IU/kg, 3 times per week).
The maximum dosage should not exceed 200 IU/kg, 3 times per week.
Adult peritoneal dialysis patients:
Where intravenous access is not readily available Epotex® Benta may be administered subcutaneously. The treatment is divided into two stages:
- Correction phase: starting dose of 50 IU/kg, 2 times per week.
- Maintenance phase: dosage adjustment in order to maintain hemoglobin values at the desired level: (Hb between 10 and 12 g/dl (6.2 - 7.5 mmol/l) (maintenance dose between 25 and 50 IU/kg 2 times per week into 2 equal injections).
Treatment of patients with chemotherapy induced anemia:
Epotex® Benta should be administered by the subcutaneous route to patients with anemia (e.g. hemoglobin concentration 10g/dl (6.2 mmol/l)). Anemia 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.
Due to intra-patient variability, occasional individual hemoglobin values for a patient above and below the desired hemoglobin level may be observed. Hemoglobin variability should be addressed through dose management, with consideration for the hemoglobin target range of 10g/dl (6.2 mmol/l) to 12g/dl (7.5mmol/l). A sustained hemoglobin level of greater than 12g/dl (7.5mmol/l) should be avoided; guidance for appropriate dose adjustment for when hemoglobin values exceed 12g/dl (7.5mmol/l) is described below.
rHuEPO Alpha therapy should continue until one month after the end of chemotherapy. The initial dose is 150 IU/kg given subcutaneously 3 times per week. Alternatively, Epotex® Benta can be administered at an initial dose of 450 IU/kg subcutaneously once weekly. If the hemoglobin has increased by at least 1 g/dl (0.62 mmol/l) or the reticulocyte count has increased 40,000 cells/µl above baseline after 4 weeks of treatment, the dose should remain at 150 IU/kg 3 times per week or 450 IU/kg once weekly. If the hemoglobin increase is <1 g/dl (<0.62 mmol/l) and the reticulocyte count has increased <40,000 cells/µl above baseline, increase the dose to 300 IU/kg 3 times per week. If after an additional 4 weeks of therapy at 300 IU/kg 3 times per week, the hemoglobin has increased 1 g/dl (0.62 mmol/l) or the reticulocyte count has increased 40,000 cells/µl, the dose should remain at 300 IU/kg 3 times per week.However, if the hemoglobin has increased <1 g/dl (<0.62 mmol/l) and the reticulocyte count has increased <40,000 cells/µl above baseline, response is unlikely and treatment should be discontinued. Patients should be monitored closely to ensure that the lowest approved dose of erythropoiesis-stimulating agent (ESA) is used to provide adequate control of the symptoms of anemia.
- Dose adjustment to maintain hemoglobin concentrations between 10g/dl – 12 g/dl: if the hemoglobin is rising by more than 2 g/dl (1.25 mmol/l) per month, or if the hemoglobin exceeds 12 g/dl (7.5 mmol/l), reduce the rHuEPO Alpha dose by about 25 - 50%. If the hemoglobin exceeds 13 g/dl (8.1 mmol/l), discontinue therapy until it falls below 12 g/dl (7.5 mmol/l) and then reinstitute rHuEPO Alpha therapy at a dose 25% below the previous dose.
Zidovudine-treated HIV-infected Patients:
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 rHuEPO Alpha is 100 IU/kg as an IV or SC injection 3 times per week for 8 weeks. Prior to beginning rHuEPO Alpha, it is recommended that the endogenous serum Erythropoietin level be determined (prior to transfusion). Available evidence suggests that patients receiving zidovudine with endogenous serum Erythropoietin levels > 500 mIU/mL is unlikely to respond to therapy with rHuEPO Alpha.
Adult surgery patients in an autologous predonation program:
The intravenous route of administration should be used. At the time of donating blood, rHuEPO Alpha should be administered after the completion of the blood donation procedure.
Mildly anemic patients (hematocrit of 33-39%) requiring predeposit of 4 units of blood should be treated with rHuEPO Alpha at 600 IU/kg, 2 times weekly for 3 weeks prior to surgery. Using this regimen, it was possible to withdraw 4 units of blood from 81% of rHuEPO Alpha-treated patients compared to 37% of placebo-treated patients. rHuEPO Alpha therapy reduced the risk of exposure to homologous blood by 50% compared to patients not receiving rHuEPO Alpha.
All patients being treated with rHuEPO Alpha should receive adequate iron supplementation (e.g. 200 mg oral elemental iron daily) throughout the course of rHuEPO Alpha treatment. Iron supplementation should be started as soon as possible, even several weeks prior to initiating the autologous predeposit, in order to achieve high iron stores prior to starting rHuEPO Alpha therapy.
Adult patients scheduled for major elective orthopedic surgery:
The subcutaneous route of administration should be used.
The recommended dose regimen is 600 IU/kg of rHuEPO Alpha, given 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, 300 IU/kg rHuEPO Alpha should be given daily for 10 consecutive days prior to surgery, on the day of surgery and for four days immediately thereafter. When performing hematologic assessments during the preoperative period, if the hemoglobin level reaches 15 g/dl, or higher, administration of rHuEPO Alpha should be stopped and further dosages should not be given.
Care should be taken to ensure that at the outset of the treatment patients are not iron deficient. All patients being treated with rHuEPO Alpha should receive adequate iron supplementation (e.g. 200 mg oral elemental iron daily) throughout the course of rHuEPO Alpha treatment. If possible, iron supplementation should be started prior to rHuEPO Alpha therapy, to achieve adequate iron stores.

OVERDOSAGE
- Overdosage: the maximum amount of rHuEPO Alpha that can be safely administered in single or multiple doses has not been determined. Doses of up to 1500 IU/kg 3 times per week for 3 to 4 weeks have been administered to adults without any direct toxic effects of Erythropoietin.
-Treatment: doses up to 1500 IU/kg 3 times per week for 3-4 week have been administered without any direct toxic effect of rHuEPO Alpha. The drug should be stopped in case of unusual increase in hematocrit level. It may result in polycythemia and hematocrit should be monitored carefully. If polycythemia is a concern, phlebotomy may be indicated to decrease hematocrit. Supportive care for hypertension or convulsion may be required in case of these symptoms due to rHuEPO Alpha overdose.

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

Date of revision: July 2012.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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