330 x 240 mm PANTONE 425 U

SENTIDO DE LECTURA PHARMACODE

BIOSIDUS

HEMAX®

RECOMBINANT HUMAN ERYTHROPOIETIN

Lyophilized injectable dosage form - Solution for injection
Made in Argentina - Prescription Drug

DESCRIPTION:
HEMAX® drug product contains erythropoietin alfa (recombinant human erythropoietin, epoetin alfa) as active ingredient. Epoetin is a 165-amino-acid glycoprotein produced by recombinant DNA technology obtained from a genetically modified mammal cell line. Epoetin has a maximum purity level and is indistinguishable from natural human erythropoietin.

COMPOSITION:
Each vial of lyophilized powder contains:
Active ingredient

	HEMAX®									
	1000 IU/mL	**2000 IU/mL**	**2000 IU/2 mL**	**3000 IU/mL**	**3000 IU/2 mL**	**4000 IU/mL**	**4000 IU/2 mL**	**10000 IU/mL**	**20000 IU/mL**	**40000 IU/ml**
Recombinant human erythropoietin	1000 IU	2000 IU	2000 IU	3000 IU	3000 IU	4000 IU	4000 IU	10000 IU	20000 IU	40000 IU

Excipients

Mannitol	25.0 mg	25.0 mg	50.0 mg	25.0 mg	50.0 mg	25.0 mg	50.0 mg	25.0 mg	25.0 mg	25.0 mg
Sodium chloride	3.2 mg	3.2 mg	6.4 mg	3.2 mg	6.4 mg	3.2 mg	6.4 mg	3.2 mg	3.2 mg	3.2 mg
Monobasic Sodium Phosphate	1.4 mg	1.4 mg	2.8 mg	1.4 mg	2.8 mg	1.4 mg	2.8 mg	1.4 mg	1.4 mg	1.4 mg
Dibasic Sodium Phosphate Dodecahydrate	4.0 mg	4.0 mg	8.0 mg	4.0 mg	8.0 mg	4.0 mg	8.0 mg	4.0 mg	4.0 mg	4.0 mg
Human Albumin	2.5 mg	2.5 mg	5.0 mg	2.5 mg	5.0 mg	2.5 mg	5.0 mg	2.5 mg	2.5 mg	2.5 mg

Each ampoule/pre-filled syringe with diluent contains:

	HEMAX®									
	1000 IU/mL	**2000 IU/mL**	**2000 IU/2 mL**	**3000 IU/mL**	**3000 IU/2 mL**	**4000 IU/mL**	**4000 IU/2 mL**	**10000 IU/mL**	**20000 IU/mL**	**40000 IU/ml**
Water for injection	1 mL	1 mL	2 mL	1 mL	2 mL	1 mL	2 mL	1 mL	1 mL	1 mL

Each vial/pre-filled syringe with solution contains:
Active ingredient:

	HEMAX® 2000 IU	**HEMAX® 4000 IU**
Recombinant human erythropoietin	2000 IU	4000 IU

Excipients

Mannitol	25.0 mg	25.0 mg
Sodium chloride	3.2 mg	3.2 mg
Monobasic sodium phosphate	1.4 mg	1.4 mg
Dibasic sodium phosphate, dodecahydrate	4.0 mg	4.0 mg
Human albumin	2.5 mg	2.5 mg
Water for injection	1.00 mL	1.00 mL

THERAPEUTIC ACTION:
ATC code: B03XA01. Anti-anaemic. Erythropoiesis-stimulating agent.

INDICATIONS:
Hemax® is indicated for:
Treatment of anaemia associated with chronic renal failure (CRF).
- Hemax® is indicated in patients on dialysis as well as in those not requiring dialysis, to enhance or maintain the red cell level (as evidenced by the haematocrit or haemoglobin determinations) and to reduce the need for transfusions. However, non-dialysis patients with symptomatic anaemia considered for Hemax® therapy should have a haemoglobin less than 10 g/dL.
- Hemax® should not be administered as an emergency transfusion substitute in patients requiring immediate correction of a severe anaemia.
- Treatment of Zidovudine-induced anaemia in HIV-infected patients. Hemax® is indicated for the treatment of anaemia associated with zidovudine therapy of HIV-infected patients to enhance or maintain the red cell level, (as evidenced by the haematocrit or haemoglobin determinations) and to reduce the need for transfusions. It is not indicated for the treatment of anaemia due to other factors (such as iron or folate deficit, haemolysis, or gastrointestinal haemorrhage) in this group of patients.
- Treatment of chemotherapy-induced anaemia in cancer patients. / Treatment of anaemia in cancer patients undergoing chemotherapy. Hemax® is indicated for the treatment of symptomatic anaemia caused by chemotherapy in patients with metastases of non-myeloid malignancies. Treatment with erythropoietin has shown to reduce the need for red blood cell transfusions in patients on concomitant chemotherapy during a minimal 2-month period.

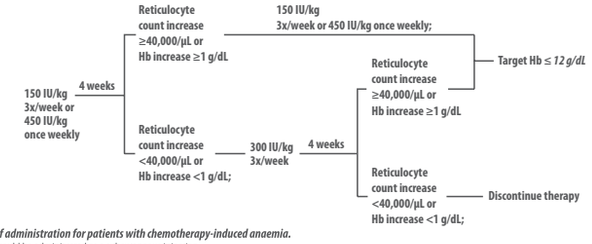
Hemax® is not indicated for patients receiving chemotherapy when the anticipated outcome is cure.
- Hemax® is indicated for the treatment of symptomatic anaemia (haemoglobin concentration ≤10 g/dL) in adults with low or intermediate-1 risk myelodysplastic syndrome (MDS) and low serum erythropoietin (<200 mU/mL).
- Hemax® is not indicated to treat anaemia related to other factors (iron or folate deficit, haemolysis, gastrointestinal haemorrhage) in this group of patients. Hemax® is not indicated in patients receiving hormone therapy, biological products or radiotherapy without concomitant bone marrow suppressive chemotherapy.
- Reduction of allogeneic blood transfusion in anaemic patients who undergo elective major orthopaedic surgery.

Hemax® is indicated in anaemic patients (haemoglobin between 10 and ≤13 g/dL) at high risk for perioperative blood loss from elective major orthopaedic, non-cardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions. It is indicated for patients at high risk for the need of perioperative transfusions with significant, anticipated blood loss.
- Treatment of anaemia in prematurity

Hemax® is indicated for the treatment of anaemia in preterm infants with a body weight between 750-1,500 g at birth and a gestational age under 34 weeks.

CLINICAL PHARMACOLOGY:
A) Mechanism of action:
Erythropoietin is a glycoprotein hormone produced mainly in the kidney in response to hypoxia and is the most important regulator of erythrocyte production. Erythropoietin induces erythropoiesis by stimulating the division and differentiation of erythroid progenitors in the bone marrow, causing the enhancement of the globular mass and, in turn, the haematocrit. Erythropoietin also stimulates the release of reticulocytes from the bone marrow into the bloodstream, where they mature into erythrocytes.
The normal concentration of endogenous erythropoietin is 10-30 mU/mL and it is regulated by the levels of tissue oxygenation. When such levels decrease, the erythropoietin concentration increases up to 100- and 1000-fold. This is also observed in anaemic patients.
Pharmacodynamic effects
Healthy volunteers
After single doses (20,000 to 160,000 IU subcutaneously) of epoetin alfa, a dose-dependent response was observed for the pharmacodynamic markers investigated, including reticulocytes, erythrocytes, and haemoglobin. A defined concentration-time profile with peak and return to baseline was observed for changes in percent reticulocytes. A less defined profile was observed for erythrocytes and haemoglobin. In general, all pharmacodynamic markers increased in a linear manner with dose reaching a maximum response at the highest dose levels.
Further pharmacodynamic studies explored 40,000 IU once weekly versus 150 IU/kg 3 times per week. Despite the differences in the time-concentration profiles, the pharmacodynamic response (determined by the changes in reticulocyte, haemoglobin and total erythrocytes percentage) was similar among these regimes. Additional studies compared the 40,000 IU once-weekly regimen of epoetin alfa with biweekly doses ranging from 80,000 to 120,000 IU subcutaneously. Overall, based on the results of these pharmacodynamic studies in healthy subjects, the 40,000 IU once-weekly dosing regimen seems to be more efficient in producing erythrocytes than the biweekly regimens despite an observed similarity in reticulocyte production in the once-weekly and biweekly regimens.
Chronic renal failure
Epoetin alfa has been shown to stimulate erythropoiesis in anaemic patients with chronic renal failure, including dialysis and pre-dialysis patients. The first evidence of a response to epoetin alfa is an increase in the reticulocyte count within 10 days, followed by increases in erythrocyte count, haemoglobin and haematocrit, usually within 2 to 6 weeks. The haemoglobin response varies between patients and may be impacted by iron stores and the presence of concurrent medical problems.**Chemotherapy-induced anaemia**
Epoetin alfa administered 3 times per week or once weekly has been shown to increase haemoglobin and decrease transfusion requirements after the first month of therapy in anaemic cancer patients receiving chemotherapy. In a study comparing the 150 IU/kg, 3 times-per-week and 40,000 IU, once-weekly dosing regimens in healthy subjects and in anaemic cancer subjects the time profiles of changes in percent reticulocytes, haemoglobin, and total erythrocytes were similar between the two dosing regimens in both healthy and anaemic cancer subjects. The areas under the curve (AUCs) of the respective pharmacodynamic parameters were similar between the 150 IU/kg, 3 times-per-week and 40,000 IU, once-weekly dosing regimens in healthy subjects and in anaemic cancer subjects.
Adult surgery patients in an autologous predonation programme
Epoetin alfa has been shown to stimulate erythrocyte production in order to augment autologous blood collection, and to limit the decline in haemoglobin in adult patients scheduled for major elective surgery who are expected to predeposit their complete perioperative blood needs. The greatest effects are observed in patients with low haemoglobin (≤13 g/dL).
Treatment of adult patients scheduled for major elective orthopaedic surgery
In patients scheduled for major elective orthopaedic surgery with a pretreatment haemoglobin of >10 to ≤13 g/dL, epoetin alfa has been shown to decrease the risk of receiving allogeneic transfusions and hasten erythroid recovery (increased haemoglobin levels, haematocrit levels, and reticulocyte counts).
B) Pharmacokinetics:
Absorption
Epoetin alfa, Hemax® active ingredient, is indicated for parenteral (subcutaneous or intravenous) administration. There was no accumulation after multiple dose administration of 600 IU/kg administered subcutaneously weekly.
The absolute bioavailability of subcutaneous injectable epoetin alfa is approximately 20% in healthy subjects. Distribution
The mean volume of distribution was 49.3 mL/kg after intravenous doses of 50 and 100 IU/kg in healthy subjects. Following intravenous administration of epoetin alfa in subjects with chronic renal failure, the volume of distribution ranged from 57-107 mL/kg after single dosing (12 IU/kg) to 42-64 mL/kg after multiple dosing (48-192 IU/kg), respectively. Thus, the volume of distribution is slightly greater than the plasma space.
The initial increase in the reticulocyte count occurs within 7 to 10 days following administration.
Red cell count, haematocrit and haemoglobin levels increase significantly generally within 2 to 6 weeks following epoetin alfa administration. The range and extent of the response depends on the dose and availability of iron stores.
The maximum plasma concentration is achieved 15 minutes following the administration of a single intravenous dose and between 5 to 24 hours following subcutaneous administration as a single dose. In this latter case, peak concentrations may remain for 12 to 16 hours and detectable amounts can be observed for at least 24 hours following administration.
Elimination
The half-life of epoetin alfa is 4 to 13 hours following intravenous or subcutaneous administration. Elimination half-life is generally longer after the administration of the first doses than after two or more weeks of treatment. Generally, after 24 hours, erythropoietin plasma levels return to their basal levels.
The mean apparent clearance (CL/F) for the 150 IU/kg 3 times-per-week and 40,000 IU once-weekly regimens in healthy subjects were 31.2 and 12.6 mL/h/kg, respectively. The mean CL/F for the 150 IU/kg, 3-times-per-week and 40,000 IU, once-weekly regimens in the anaemic cancer subjects were 45.8 and 11.3 mL/h/kg, respectively. In most anaemic subjects with cancer receiving cyclic chemotherapy, the CL/F was lower after subcutaneous doses of 40,000 IU once weekly and 150 IU/kg, 3 times per week compared with the values for healthy subjects.
In studies on adult healthy volunteers, the half-life following intravenous administration is 20% lower than in patients with renal failure. In a trial that involved healthy volunteers, Hemax® half-life, administered by subcutaneous route, was 20.8 ± 6.3 hours.
Once the treatment is discontinued, haematocrit may start decreasing after 2 weeks.
In healthy subjects, a dose-proportional increase in serum epoetin alfa concentrations was observed after intravenous administration of 150 and 300 IU/kg, 3 times per week. Subcutaneous administration of single doses of 300 to 2,400 IU/kg epoetin alfa resulted in a linear relationship between mean C_{max} and dose, and between mean AUC and dose. An inverse relationship between apparent clearance and dose was noted in healthy subjects.
Pharmacokinetic/pharmacodynamic correlation
Epoetin alfa exhibits a dose-related effect on haematological parameters, which is independent of route of administration.
Paediatric population
A half-life of approximately 6.2 to 8.7 hours has been reported in paediatric subjects with chronic renal failure following multiple dose intravenous administration of epoetin alfa. The pharmacokinetic profile of epoetin alfa in children and adolescents appears to be similar to that of adults.
Pharmacokinetic data in neonates is limited.
Renal insufficiency
In chronic renal failure patients, the half-life of intravenously administered epoetin alfa is slightly prolonged, approximately 5 hours, compared to healthy subjects.

THERAPEUTIC USE AND DOSAGE:
A) Treatment of anaemia associated with chronic renal failure:
Chronic renal failure (CRF) is the clinical condition in which there is a progressive and usually irreversible decline in kidney function. Epoetin therapy has been shown to stimulate erythropoiesis in anaemic patients with CRF, including dialysis and pre-dialysis patients. The first evidence of a stimulation of erythropoiesis is an increase in the reticulocyte count after 8 days of treatment, followed by increases in haemoglobin and haematocrit, within 2 to 6 weeks. The rate and extent of this increase depend on the initial epoetin alfa dose, baseline haematocrit and haemoglobin levels, availability of iron stores, and the presence of concurrent medical problems that may blunt treatment responsiveness (infectious/inflammatory episodes, etc.).
Before beginning treatment with Hemax®, other causes of anaemia must be ruled out (e.g. folic acid or Vitamin B_{12} deficiencies, aluminium intoxication, infection or inflammation, blood loss, haemolysis and bone marrow fibrosis of any origin) and correct concomitant factors that may aggravate the anaemia, specially, iron deficiency. Therefore, studies on iron metabolism should be conducted, including iron concentration in blood, total saturation capacity, transferrin saturation percentage, and serum ferritin. Transferrin saturation should be at least 20%, and ferritin should be at least 100 ng/mL prior to treatment with Hemax®. Iron levels must be monitored and maintained at adequate levels during treatment with epoetin.
Blood pressure should be adequately controlled prior to initiation of therapy and must be closely monitored during therapy.
The recommended desired haemoglobin concentration range is between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L). Hemax® should be administered in order to increase haemoglobin to not greater than 12 g/dL (7.5 mmol/L). A rise in haemoglobin of greater than 2 g/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 haemoglobin values for a patient above and below the desired haemoglobin concentration range may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin concentration range of 10 g/dL (6.2 mmol/L) to 12 g/dL (7.5 mmol/L).
A sustained haemoglobin level of greater than 12 g/dL (7.5 mmol/L) should be avoided. If the haemoglobin is rising by more than 2 g/dL (1.25 mmol/L) per month, or if the sustained haemoglobin exceeds 12 g/dL (7.5 mmol/L) reduce the Hemax® dose by 25%. If the haemoglobin exceeds 13 g/dL (8.1 mmol/L), discontinue therapy until it falls below 12 g/dL (7.5 mmol/L) and then reinstitute Hemax® therapy at a dose 25% below the previous dose.
Patients should be closely monitored to ensure that the lowest effective dose of Hemax® is used to provide adequate control of anaemia and of the symptoms of anaemia whilst maintaining a haemoglobin concentration below or at 12 g/dL (7.5 mmol/L).
In patients with a poor haemoglobin response to ESA, alternative explanations for the poor response should be considered.
Treatment with Hemax® is divided into two stages: correction and maintenance phase.
Adult haemodialysis patients
In patients on haemodialysis where intravenous access is readily available, administration by the intravenous route is preferable.
Correction phase
The recommended starting dose in adult haemodialysis patients is 50 IU/kg/dose administered intravenously or 40 IU/kg/dose subcutaneously, 3 times per week. After four weeks of treatment, the dose should be corrected according to the haemoglobin level increase:
a) If increase equals 1 g/dL or above: maintain the same dose.
b) If increase is below 1 g/dL: increase the dose by 25 IU/kg/dose increments (3 times per week) until the desired haemoglobin concentration range between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L) is achieved.
The recommended total weekly dose is between 75 IU/kg and 300 IU/kg.
Patients with very low initial haemoglobin (<6 g/dL or <3.75 mmol/L) may require higher maintenance doses than patients whose initial anaemia is less severe (>8 g/dL or >5 mmol/L).
Maintenance phase
Once the target value has been achieved, the dose can be reduced by 30% and administration may be by subcutaneous route if the patient had started intravenous treatment. The maintenance dose must be individualised for each patient. Ten percent of patients on dialysis require 25 IU/kg/dose 3 times weekly and another 10% requires 200 IU/kg/dose 3 times weekly; the average maintenance dose is 75 IU/kg/dose 3 times weekly. Dose adjustments should be performed between intervals not shorter than 4 weeks, since response to dose changes is evidenced after 2 to 6 weeks.
Paediatric haemodialysis patients
Anaemia symptoms and sequelae may vary with age, sex, and other medical conditions; a physician's evaluation of the individual patient's clinical course and condition is necessary.
In paediatric patients, the recommended haemoglobin concentration range is between 9.5 g/dL to 11 g/dL (5.9 to 6.8 mmol/L). Hemax® should be administered in order to increase haemoglobin to not greater than 11 g/dL (6.8 mmol/L). A rise in haemoglobin of greater than 2 g/dL (1.25 mmol/L) over a four-week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.
Patients should be closely monitored to ensure that the lowest approved dose of Hemax® is used to provide adequate control of anaemia and of the symptoms of anaemia.
Treatment with Hemax® is divided into two stages: correction and maintenance phase.
In paediatric patients on haemodialysis where vascular access is readily available, administration by the intravenous route is preferable.
Correction phase
The starting dose is 50 IU/kg intravenously, 3 times per week.
If necessary, increase or decrease the dose by 25 IU/kg (3 times per week) until the desired haemoglobin concentration range of between 9.5 g/dL to 11 g/dL (5.9 to 6.8 mmol/L) is achieved (this should be done in steps of at least four weeks).
Maintenance phase
Appropriate adjustment of the dose should be made in order to maintain haemoglobin levels within the desired concentration range between 9.5 g/dL to 11 g/dL (5.9 to 6.8 mmol/L).
Generally, children under 30 kg require higher maintenance doses than children over 30 kg and adults.
Paediatric patients with very low initial haemoglobin (<6.8 g/dL or <4.25 mmol/L) may require higher maintenance doses than patients whose initial haemoglobin is higher (>6.8 g/dL or >4.25 mmol/L).
Adult chronic renal failure patients not on dialysis
Patients with chronic renal failure not requiring dialysis respond to therapy in a manner similar to that observed in patients on dialysis. The recommended doses are between 75 and 100 IU/kg/week; the subcutaneous route is recommended.
Correction phase
Starting dose of 50 IU/kg, 3 times per week, followed if necessary, by a dose increase with 25 IU/kg increments (3 times per week) until the desired target is achieved (this should be done in steps of at least four weeks).
Maintenance phase
During the maintenance phase, Hemax® can be administered either 3 times per week, and in the case of subcutaneous administration, once weekly or once every 2 weeks.
Appropriate adjustment of dose and dose intervals should be made in order to maintain haemoglobin values at the desired level: haemoglobin between 10 g/dL and 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, 240 IU/kg (up to a maximum of 20,000 IU) once weekly, or 480 IU/kg (up to a maximum of 40,000 IU) once every 2 weeks.
Anaemic chronic renal failure paediatric patients before initiation of dialysis or on peritoneal dialysis
The safety and efficacy of Hemax® have not been established in chronic renal failure patients with anaemia before initiation of dialysis or on peritoneal dialysis. No dosing recommendation can be made.
Method of administration for adult chronic renal failure patients with symptomatic anaemia.
In patients with chronic renal failure where intravenous access is routinely available (haemodialysis patients) administration of Hemax® by the intravenous route is preferable.
Where intravenous access is not readily available (patients not yet undergoing dialysis and peritoneal dialysis patients), it may be administered as a subcutaneous injection.
Method of administration for paediatric chronic renal failure patients on haemodialysis with symptomatic anaemia.
In paediatric patients with chronic renal failure where intravenous access is routinely available (haemodialysis patients), administration of Hemax® by the intravenous route is preferable.
B) Adult patients on peritoneal dialysis
Where vascular access is not readily available, Hemax® may be administered subcutaneously.
Correction phase
The starting dose is 50 IU/kg, twice weekly.
Maintenance phase
The recommended maintenance dose is between 25 IU/kg and 50 IU/kg, twice weekly in 2 equal injections.
Appropriate adjustment of the dose should be made in order to maintain haemoglobin values at the desired level between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L).
C) HIV-infected patients treated with Zidovudine:
Hemax® reduces transfusion requirements and increases haematocrit level in zidovudine-treated HIV-infected patients, resulting in a significant improvement in the quality of life. Patients with endogenous erythropoietin levels ≤500 mU/mL respond better to treatment, so an erythropoietin dosage is recommended before beginning therapy.
The recommended initial dose is 100 IU/kg/dose in adults and 150 IU/kg/dose in children, 3 times per week, intravenously or subcutaneously, for 8 weeks. Response can be assessed after 4 weeks of treatment. If no satisfactory response is obtained, this dose can be escalated by 50 IU/kg increases to a maximum of 300 IU/kg 3 times per week.
Response to epoetin treatment may decrease in case of infectious or inflammatory conditions.
If haematocrit is above 40%, administration of Hemax® can be interrupted until such value reaches 36%. The dose must be reduced by 25% when treatment is re-initiated and thereafter, followed by evaluation through the target haematocrit level.
D) Anaemia in cancer patients on chemotherapy:
Anaemia symptoms and sequelae may vary with age, sex, and other medical conditions; a physician's evaluation of the individual patient's clinical course and condition is necessary. In this patient population, epoetin increases haematocrit and reduces the transfusion requirements between the first and fourth month of treatment.
Appropriate adjustment of the dose should be made in order to maintain haemoglobin concentrations within the desired concentration range between 10 g/dL to 12 g/dL (6.2 to 7.5 mmol/L).
Due to intra-patient variability, occasional individual haemoglobin concentrations for a patient above and below the desired haemoglobin concentration range may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the desired haemoglobin concentration range between 10 g/dL (6.2 mmol/L) to 12 g/dL (7.5 mmol/L). A sustained haemoglobin concentration higher than 12 g/dL (7.5 mmol/L) should be avoided; guidance for appropriate dose adjustment for when haemoglobin concentrations exceed 12 g/dL (7.5 mmol/L) are described below.
If the haemoglobin concentration 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 haemoglobin concentration 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 haemoglobin concentration 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.
If the haemoglobin concentration 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.
Hemax® therapy should be discontinued if the haemoglobin concentration level exceeds 13 g/dL and reinitiated at a dose 25% below the previous dose when it has dropped below 12 g/dL. Hemax therapy should continue until approximately 4 weeks after the end of chemotherapy.
If patients have not responded satisfactorily to a weekly dose of 60,000 IU 4 four weeks, it is unlikely that they will respond to higher doses of Hemax®. Therefore, therapy should be discontinued.
Treatment of paediatric patients with chemotherapy-induced anaemia
The safety and efficacy of Hemax® in paediatric patients receiving chemotherapy have not been established.
Dose adjustment to maintain haemoglobin concentrations between 10 g/dL to 12 g/dL
If the haemoglobin concentration is increasing by more than 2 g/dL (1.25 mmol/L) per month, or if the haemoglobin concentration level exceeds 12 g/dL (7.5 mmol/L), reduce the Hemax® dose by about 25 to 50%.
If the haemoglobin concentration level exceeds 13 g/dL (8.1 mmol/L), discontinue therapy until it falls below 12 g/dL (7.5 mmol/L) and then reinitiate Hemax® therapy at a dose 25% below the previous dose.
The recommended dosing regimen is described in the following diagram:



Method of administration for patients with chemotherapy-induced anaemia.
Hemax® should be administered as a subcutaneous injection.
D) Autologous transfusion:
In patients scheduled for elective surgery (hip, knee, etc.) in an autologous predonation programme, the use of epoetin alfa has been shown to decrease the need of allogeneic transfusions. Mildly anaemic patients (haematocrit of 33 to 39%) requiring predeposit of ≥4 units of blood should be treated with Hemax® 600 IU/kg intravenously, twice weekly for 3 weeks prior to surgery. The main predictive variable for treatment response is haemoglobin level before surgery; patients with levels between 10 and 13 g/dL are most benefited by this therapy. Initial dose is 300 IU/kg/day subcutaneously, beginning 10 days before surgery and continuing up to 4 days after surgery. As an alternative, single weekly doses at 600 IU/kg subcutaneously can be used on days 21, 14 and 7 prior to surgery and the fourth dose should be administered on surgery day.
All patients must receive an appropriate iron supplement, which should be administered not later than Hemax® treatment has been initiated and should be continued through the epoetin treatment course.
Treatment of paediatric surgery patients in an autologous predonation programme
The safety and efficacy of Hemax® in paediatrics have not been established.
No data are available.
Method of administration for adult patients in an autologous predonation programme.
Hemax® should be administered by the intravenous route.
E) Treatment of adult patients scheduled for major elective orthopaedic surgery
The recommended dose of Hemax® is 600 IU/kg 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 3 weeks, Hemax® 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 haemoglobin level reaches 15 g/dL, or higher, during the preoperative period, administration of Hemax® should be stopped and further dosages should not be administered.
Treatment of paediatric patients scheduled for major elective orthopaedic surgery
The safety and efficacy of Hemax® in paediatrics have not been established.
No data are available.
Method of administration for adult patients scheduled for major elective orthopaedic surgery
Hemax® should be administered as a subcutaneous injection.
F) Treatment of adult patients with low/intermediate-1-risk myelodysplastic syndrome (MDS)
Hemax® should be administered to patients with symptomatic anaemia (e.g. haemoglobin concentration ≤10 g/dL (6.2 mmol/L)).
The recommended starting dose is Hemax® 450 IU/kg (maximum total dose is 40,000 IU) administered subcutaneously once every week, with not less than 5 days between doses. Appropriate dose adjustments should be made to maintain haemoglobin concentrations within the target range of 10 g/dL to 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 (see diagram below). A haemoglobin concentration of greater than 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 haemoglobin 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: Epoetin alfa should be withheld when the haemoglobin concentration exceeds 12 g/dL (7.5 mmol/L). Once the haemoglobin level is <11 g/dL the dose can be restarted on the same dosing step or one dosing step down based on physician judgment. Decreasing the dose by one dosing step should be considered if there is a rapid increase in haemoglobin (>2 g/dL over 4 weeks).
Anaemia symptoms and sequelae may vary with age, sex, and other medical conditions; a physician's evaluation of the individual patient's clinical course and condition is necessary.

Method of administration for adult patients with low/intermediate-1-risk myelodysplastic syndrome
Hemax® should be administered as a subcutaneous injection.
G) Anaemia of prematurity:
The use of Hemax® in anaemia of prematurity reduces transfusion requirement, measured both as number of transfused patients and transfused blood volume.
The recommended dose is 250 IU/kg administered subcutaneously 3 times per week, from the second week of life and over eight weeks.
METHOD OF ADMINISTRATION
Precautions to be taken before handling or administering the medicinal product. Before use, allow the Hemax® syringe to reach room temperature. This usually takes between 15 and 30 minutes. **Intravenous 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 to rinse the tubing and ensure satisfactory injection of the product into the circulation.
A slower administration is preferable in patients who react to the treatment with "flu-like" symptoms.
Do not administer Hemax® by intravenous infusion or in conjunction with other drug solutions.
Subcutaneous administration
A maximum volume of 2 mL at one injection site should generally not be exceeded. The injections 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 Hemax® subcutaneously themselves, instruction as to the proper dosage and administration should be provided.
As with any other injectable product, check that there are no particles in the solution or change in colour.

CONTRAINDICATIONS:
Hemax® is contraindicated in patients with:
1. Uncontrolled hypertension.
2. Pure red cell aplasia following treatment with epoetin alfa.
3. Known hypersensitivity to human albumin.
4. Known hypersensitivity to mammalian cell-derived products.
5. Hypersensitivity to the active ingredient or to any of the excipients.
6. Contraindications associated with autologous blood predonation programmes.
7. Use of Hemax® in patients scheduled for major elective orthopaedic surgery not 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.
8. Surgery patients who for any reason cannot receive adequate antithrombotic prophylaxis.

ADVERSE REACTIONS
Summary of the safety profile
The most frequent adverse drug reaction during treatment with epoetin alfa is a dose-dependent increase in blood pressure or aggravation of existing hypertension. Monitoring of the blood pressure should be performed, particularly at the start of therapy.
The most frequently occurring adverse drug reactions observed in clinical trials with epoetin alfa are diarrhoea, nausea, vomiting, pyrexia, and headache. Influenza-like illness may occur especially at the start of treatment.
Respiratory tract congestion, which includes events of upper respiratory tract congestion, nasal congestion and nasopharyngitis, have been reported in studies with extended interval dosing in adult patients with renal failure not yet undergoing dialysis.
An increased incidence of thrombotic vascular events (TVEs) has been observed in patients receiving ESAs as epoetin alfa.

Tabulated List of Adverse Reactions
Frequency estimate: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very Rare (<1/10,000), not known (cannot be estimated from the available data).

MedDRA System Organ Classification (SOC)	Adverse Reaction	Frequency
Blood and lymphatic system disorders	Pure red cell aplasia, Thrombocythemia	Rare
Metabolism and nutrition disorders	Hyperkalaemia[1]	Uncommon
Immune system disorders	Hypersensitivity	Uncommon
	Anaphylactic reaction	Rare
Nervous system disorders	Headache	Common
	Convulsion	Uncommon
Vascular disorders	Hypertension, Venous and arterial thromboses[2]	Common
	Hypertensive crisis	Not known
Respiratory, thoracic and mediastinal disorders	Cough	Common
	Respiratory tract congestion	Uncommon
Gastrointestinal disorders	Diarrhoea, nausea, vomiting	Very common
Skin and subcutaneous tissue disorders	Rash	Common
	Urticaria	Uncommon
	Angioneurotic oedema	Not known
Musculoskeletal and connective tissue disorders	Arthralgia, bone pain, myalgia, pain in extremity	Common
Congenital, familial and genetic disorders	Porphyria acute	Rare
General disorders and administration site conditions	Pyrexia	Very common
	Chills, Influenza like illness, injection site reaction, oedema peripheral	Common
	Drug ineffective	Not known
Investigations	Anti-erythropoietin antibody positive	Rare

1. Common in dialysis
2. Includes arterial and venous, fatal and non-fatal events, such as deep venous thrombosis, pulmonary emboli, retinal thrombosis, arterial thrombosis (including myocardial infarction), cerebrovascular accidents (including cerebral infarction and cerebral haemorrhage) transient ischaemic attacks, and shunt thrombosis (including dialysis equipment) and thrombosis within arteriovenous shunt aneurisms.

Description of selected adverse reactions
Hypersensitivity reactions, including cases of rash (including urticaria), anaphylactic reactions, and angiooedema have been reported.
Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have occurred also during epoetin alfa 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.
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.
Antibody-mediated pure red cell aplasia has been very rarely reported in <1/10,000 cases per patient year after months to years of treatment with epoetin alfa.
Chronic Renal Failure Patients:
a) Hypertension:
Over 80% of patients on haemodialysis have history of arterial hypertension. When epoetin alfa therapy begins, patients' blood pressure should be controlled adequately, and antihypertensive therapy and dietary restrictions should be adjusted. Approximately 25% of patients on epoetin alfa experience increases in blood pressure, requiring an adjustment of antihypertensive medication. There is a possible relationship between the rate of rise of haematocrit and the exacerbation of blood pressure, so it is recommended that the dose of Hemax® be decreased if haematocrit increased more than 2 points over a 4-week period.
b) Pure red cell aplasia
Since epoetin alfa is a protein, some patients may develop antibodies to Hemax®. Some cases of pure red cell aplasia have been associated with neutralizing antibodies with epoetin alfa containing products. This has been reported in patients with renal failure who received the drug by subcutaneous route. These patients cannot receive Hemax® or any other epoetin-containing product.
c) Thrombotic events:
An increase in thrombotic events has been reported in dialysis patients with evident cardiovascular disease receiving epoetin alfa. These included vascular access thrombosis, acute myocardial infarction and others. Thrombotic events were observed in patients assigned to reach target haematocrit values above 40%. Moreover, this group showed higher mortality rates.
During dialysis, patients may require increased heparin doses to prevent venous access thrombosis.
Haemoglobin levels above 12 g/dL may be associated to a higher risk of cardiovascular events.
d) Seizures:
In clinical trials with epoetin alfa, 2.5% of the treated adult patients on dialysis had seizures generally associated with arterial hypertension crisis. Blood pressure should be closely monitored before and during treatment. Caution should be taken when administering epoetin alfa to patients with history of seizures.
Paediatric chronic renal failure patients on haemodialysis
The exposure of paediatric patients with chronic renal failure on haemodialysis in clinical trials and post-marketing experience is limited. No paediatric-specific adverse reactions not mentioned previously in the table above, or any that were not consistent with the underlying disease were reported in this population.
Adult patients with low/intermediate-1-risk *myelodysplastic syndrome*
In a clinical trial, subjects (4.7%) experienced thrombotic vascular events (sudden death, ischaemic stroke, embolism, and phlebitis). All thrombotic vascular events (TVEs) occurred in the epoetin alfa group and in the first 24 weeks of the study. Three were confirmed TVEs and in the remaining case (sudden death), the thromboembolic event was not confirmed. Two subjects had significant risk factors (atrial fibrillation, heart failure and thrombophlebitis).
Zidovudine-treated HIV-infected patients:
In contrast to renal failure patients, exacerbation of arterial hypertension, seizures and thrombotic events have not been reported for this group.

Cancer patients on chemotherapy:
A higher incidence of thrombotic events and increase of mortality has been observed in patients with breast cancer on chemotherapy, assigned to epoetin alfa treatment to maintain high haemoglobin levels (12 to 14 g/dL).
Albumin (human)
Hemax® contains albumin, a derivative of human blood. The risk for transmission of viral diseases is considered extremely remote based on the albumin obtention and manufacturing process of the product. The theoretical risk for the transmission of the Creutzfeldt-Jakob disease is also considered extremely remote. No cases of transmission of viral diseases have ever been identified for albumin.

WARNINGS:
General
In all patients receiving epoetin alfa, blood pressure should be closely monitored and controlled as necessary. Epoetin alfa should be used with caution in the presence of untreated, inadequately treated or poorly controllable hypertension. It may be necessary to add or increase anti-hypertensive treatment. If blood pressure cannot be controlled, epoetin alfa treatment should be discontinued.
Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have occurred also during epoetin alfa 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.
Epoetin alfa 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 infections and brain metastases.
Epoetin alfa should be used with caution in patients with chronic liver failure. The safety of epoetin alfa has not been established in patients with hepatic dysfunction.
An increased incidence of thrombotic vascular events (TVEs) has been observed in patients receiving ESAs. These include venous and arterial thromboses and embolism (including some with fatal outcomes), 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.
The reported risk of these TVEs should be carefully weighed against the benefits to be derived from treatment with epoetin alfa particularly in patients with pre-existing risk factors for TVE, including obesity and prior history of TVEs (e.g., deep venous thrombosis, pulmonary embolism, and cerebral vascular accident).
In all patients, haemoglobin levels should be closely monitored due to a potential increased risk of thromboembolic events and fatal outcomes when patients are treated at haemoglobin levels above the concentration range for the indication of use.
There may be a moderate dose-dependent rise in the platelet count within the normal range during treatment with epoetin alfa. This regresses during continued therapy. In addition, thrombocytopenia above the normal range has been reported. It is recommended that the platelet count be regularly monitored during the first 8 weeks of therapy.
All other causes of anaemia (iron, folate or Vitamin B_{12} 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 epoetin alfa, and when deciding to increase the dose. In most cases, the ferritin values in the serum fall simultaneously with the rise in haematocrit. In order to ensure optimum response to epoetin alfa, adequate iron stores should be assured, and iron supplementation should be administered if necessary.
Renal failure
In two clinical trials, patients experienced an increased risk of mortality and of occurrence of serious cardiovascular events when administered erythropoiesis-stimulating agents to target higher versus lower haemoglobin values (13.5 vs 11.3 g/dL; 14 vs 10 g/dL). It is recommended to individualize the dose with the aim of attaining and maintaining the haemoglobin level in the range 10 to 12 g/dL.
For chronic renal failure patients, iron supplementation (elemental iron 200 to 300 mg/day orally for adults and 100 to 200 mg/day orally for paediatrics) is recommended if serum ferritin levels are below 100 ng/mL.
Treatment of symptomatic anaemia in adult and paediatric chronic renal failure patients
Chronic renal failure patients being treated with epoetin alfa should have haemoglobin levels measured on a regular basis until a stable level is achieved, and periodically thereafter.
In chronic renal failure patients, the rate of increase in haemoglobin should be approximately 1 g/dL (0.62 mmol/L) per month and should not exceed 2 g/dL (1.25 mmol/L) per month to minimise risks of an increase in blood pressure.
In chronic renal failure patients, maintenance haemoglobin concentration should not exceed the upper safety limit of the haemoglobin concentration range, as recommended in section THERAPEUTIC USE AND DOSAGE. In clinical trials, an increased risk of death and serious cardiovascular events was observed when ESAs were administered to achieve a haemoglobin concentration level of greater than 12 g/dL (7.5 mmol/L).
Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when haemoglobin concentration is increased beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.
Caution should be exercised with escalation of Hemax® doses in patients with chronic renal failure since high cumulative epoetin doses may be associated with an increased risk of mortality, serious cardiovascular and cerebrovascular events. In patients with a poor haemoglobin response to epoetins, alternative explanations for the poor response should be considered.
Chronic renal failure patients treated with epoetin alfa by the subcutaneous route should be monitored regularly for loss of efficacy, defined as absent or decreased response to epoetin alfa treatment in patients who previously responded to such therapy. This is characterised by a sustained decrease in haemoglobin despite an increase in epoetin alfa dosage.
Some patients with more extended dosing intervals (greater than once weekly) may not maintain adequate haemoglobin levels and may require an increase in epoetin alfa dose. Haemoglobin levels should be monitored regularly.
Shunt thromboses have occurred in haemodialysis patients, especially in those who tend to hypotension or whose arteriovenous fistulae exhibit complications (e.g. stenoses, aneurysms, etc.). Early shunt revision and thrombosis prophylaxis by administration of acetylsalicylic acid, for example, is recommended in these patients.
Hyperkalaemia has been observed in isolated cases though causality has not been established. Serum electrolytes should be monitored in chronic renal failure patients. If an elevated or rising serum potassium level is detected, then in addition to appropriate treatment of the hyperkalaemia, consideration should be given to ceasing epoetin alfa administration until the serum potassium level has been corrected.
An increase in heparin dose during haemodialysis is frequently required during therapy with epoetin alfa as a result of the increased packed cell volume. Occlusion of the dialysis system is possible if heparinisation is not optimum.
Based on information available to date, correction of anaemia with epoetin alfa in adult patients with chronic renal failure not yet undergoing dialysis does not accelerate the rate of progression of renal failure.
Patients with cancer diagnosis
The use of ESAs shortened overall survival and/or increased the risk of tumour progression or recurrence in some clinical trials in patients with breast, head and neck, lymphoid, (non-small cell) lung, and cervical cancers.
In cancer patients, whose transferrin saturation is less than 20%, supplemental iron should be administered (iron 200 to 300 mg/day orally).
To minimise these risks, as well as the risk of serious cardiovascular events, it is recommended that the lower dose be used to avoid blood transfusion. To minimise these risks, the level of haemoglobin should not exceed 12 g/dL.
Use only for treatment of anaemia due to concomitant myelosuppressive chemotherapy and discontinue following the completion of a chemotherapy course.
Epoetin is not indicated for patients receiving chemotherapy when the anticipated outcome is cure.
Treatment of patients with chemotherapy-induced anaemia
Cancer patients being treated with epoetin alfa should have haemoglobin levels measured on a regular basis until a stable level is achieved, and periodically thereafter.
Epoetins are growth factors that primarily stimulate erythrocyte production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells. As with all growth factors, there is a concern that epoetins could stimulate the growth of tumours.
The role of ESAs on tumour progression or reduced progression-free survival cannot be excluded. In controlled clinical studies, use of epoetin alfa and other ESAs have been associated with decreased locoregional tumour control or decreased overall survival:
- Decreased locoregional control in patients with advanced head and neck cancer receiving radiation therapy when administered to achieve a haemoglobin concentration level of greater than 14 g/dL (8.7 mmol/L).
- Shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to achieve a haemoglobin concentration range of 12 to 14 g/dL (7.5 to 8.7 mmol/L).
- Increased risk of death when administered to achieve a haemoglobin concentration level of 12 g/dL (7.5 mmol/L) in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for use in this patient population.
- An observed 9% increase in risk for disease progression or death in the epoetin alfa plus standard treatment group from a primary analysis and a 15% increased risk that cannot be statistically ruled out in patients with metastatic breast cancer receiving chemotherapy when administered to achieve a haemoglobin concentration range of 10 to 12 g/dL (6.2 to 7.5 mmol/L).

In view of the above, in some clinical situations blood transfusion should be the preferred treatment for the management of anaemia in patients with cancer. The decision to administer recombinant erythropoietin treatment should be based on a benefit-risk assessment with the participation of the patient, which should consider the specific clinical context. Factors that should be considered in this assessment should include the type of tumour and its stage; the degree of anaemia; life expectancy; the environment in which the patient is being treated; and patient preference.
In cancer patients receiving chemotherapy, the 2 to 3-week delay between ESA administration and the appearance of erythropoietin-induced red cells should be taken into account when assessing if epoetin alfa therapy is appropriate (patient at risk of being transfused).
Patients receiving erythropoiesis-stimulating agents prior to surgery to reduce the number of allogeneic transfusions:
An increased rate of deep venous thrombosis in patients not receiving prophylactic anticoagulation has been reported. Prophylactic anticoagulation should be considered when an erythropoiesis-stimulating agent is indicated to reduce the number of allogeneic transfusions.
Patients included in an autologous blood predonation programme
For patients in an autologous predonation programme, iron supplementation (elemental iron 200 mg/day orally) should be administered several weeks prior to initiating the autologous predeposit in order to achieve high iron stores prior to starting epoetin alfa therapy, and throughout the course of epoetin alfa therapy.
All special warnings and special precautions associated with autologous predonation programmes, especially routine volume replacement, should be respected.
Patients scheduled for major elective orthopaedic surgery
For patients scheduled for major elective orthopaedic surgery, iron supplementation (elemental iron 200 mg/day orally) should be administered throughout the course of epoetin alfa therapy. If possible, iron supplementation should be initiated prior to starting epoetin alfa therapy to achieve adequate iron stores.
Good blood management practices should always be used in the perisurgical setting.
Patients scheduled for major elective orthopaedic surgery should receive adequate antithrombotic prophylaxis, as thrombotic and vascular events may occur in surgical patients, especially in those with underlying cardiovascular disease. In addition, special precaution should be taken in patients with predisposition for development of deep venous thrombosis (DVTs). Moreover, in patients with a baseline haemoglobin of >13 g/dL, the possibility that epoetin alfa treatment may be associated with an increased risk of postoperative thrombotic/vascular events cannot be excluded. Therefore, epoetin alfa should not be used in patients with baseline haemoglobin >13 g/dL.

PRECAUTIONS:
Immunogenicity
As for any product with parenteral administration, appropriate precautions should be attended in case allergic reactions occur after Hemax® administration. In clinical trials, minor and transient allergic reaction have been reported.
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. More severe cases have been observed with long-acting ESAs.
At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, Hemax® should be withdrawn immediately and an alternative treatment considered.
If the patient has developed a severe cutaneous skin reaction such as SJS or TEN due to the use of Hemax®, treatment with Hemax® must not be restarted in this patient at any time.
Haematology:
Exacerbation of porphyria has been reported in dialysis patients treated with epoetin alfa. Although this event is rare, it should be considered in patients with history of porphyria.
In order to improve the traceability of erythropoiesis-stimulating agents (ESAs), the trade name of the administered ESA should be clearly recorded (or stated) in the patient file.
Patients should only be switched from one ESA to another under appropriate supervision.

Pure red cell aplasia
Antibody-mediated pure red cell aplasia (PRCA) has been reported after months to years of subcutaneous epoetin treatment mainly in chronic renal failure patients. Cases have also been reported in patients with hepatitis C treated with interferon and ribavirin, when ESAs are used concomitantly. Epoetin alfa is not approved in the management of anaemia associated with hepatitis C.
In patients developing sudden lack of efficacy defined by a decrease in haemoglobin (1 to 2 g/dL per month) with increased need for transfusions, a reticulocyte count should be obtained and typical causes of non-response (e.g. iron, folate or Vitamin B_{12} deficiency, aluminium intoxication, infection or inflammation, blood loss, haemolysis and bone marrow fibrosis of any origin) should be investigated.
A paradoxical decrease in haemoglobin and development of severe anaemia associated with low reticulocyte counts should prompt to discontinue treatment with epoetin alfa and perform anti-erythropoietin antibody testing. A bone marrow examination should also be considered for diagnosis of PRCA.
No other ESA therapy should be commenced because of the risk of cross-reaction.
Lack or Loss of Response:
In patients receiving maintenance doses, who show loss or lack of response to epoetin alfa, the following causes should be ruled out:
1. Iron deficiency
2. Infection, inflammation or neoplasia.
3. Faecal Occult blood loss
4. Bone marrow dysfunction due to underlying hematologic diseases (thalassemia, myelodysplastic disorders, etc.)
5. Haemolysis
6. Aluminium intoxication
7. Vitamin B_{12} or folic acid deficiencies
8. Cystic fibrosis
9. Pure red cell aplasia

Iron supplementation:
Iron requirements may increase if existing iron stores were used for erythropoiesis and some patients may need iron supplementation. In some patients, oral iron supplementation may be insufficient and may require intravenous administration of iron sucrose.

Drug interaction:
No evidence of interaction of HEMAX® with other drugs is available.
Drugs that decrease erythropoiesis may reduce the response to epoetin alfa.
Since cyclosporine is bound by red blood cells, there is potential for a drug interaction. If epoetin alfa is given concomitantly with cyclosporine, blood levels of cyclosporine should be monitored, and the dose of cyclosporine adjusted as the haematocrit rises.
There is no evidence of interaction between epoetin alfa and G-CSF or GM-CSF with regard to haematological differentiation or proliferation of tumour in biopsy specimens.
In adult female patients with metastatic breast cancer, subcutaneous co-administration of 40,000 IU/mL epoetin alfa with trastuzumab 6 mg/kg had no effect on the pharmacokinetics of trastuzumab.
Carcinogenesis and mutagenesis:
The carcinogenetic potential of Hemax® has not been evaluated. Epoetin alfa does not induce bacterial gene mutations or chromosomal aberrations in mammalian cells.
Fertility, pregnancy, and lactation
Fertility:
In female rats treated with intravenous doses of 100 a 500 IU/kg epoetin alfa, there was a trend for slightly increased foetal wastage.
Pregnancy:
There are no enough trials on the use of Hemax® during pregnancy; therefore, this product should only be used when the potential benefit justifies the potential risk to foetus.
The use of epoetin alfa is not recommended in pregnant surgical patients participating in an autologous blood predonation programme. In pregnant rats, increase of foetal loss was observed. No adverse effects were observed in rabbits treated with doses of 500 IU/kg.
Lactation:
Human erythropoietin is a normal component of human milk, although its role has not been clearly determined. It is not known whether Hemax® is excreted in human milk. Since many drugs are, caution should be exercised when Hemax® is administered to a nursing woman.
Paediatric use:
Although multiple studies have been conducted on new-borns, breast-feeding babies and older children showing that Hemax® is effective and safe in preventing and treating anaemia, the long-term safety of this product has not been established.
Laboratory Monitoring:
After beginning treatment, haemoglobin or haematocrit should be determined twice a week until it has achieved the desired range (10 to 12 g/dL, or 30 to 36%, respectively). Once that value has been achieved, weekly controls should be carried out, for four weeks, to determine that the value has stabilized. Haemoglobin should then be monitored at regular intervals. Platelet, while blood cells and red blood cells counts, and determination of haemoglobin concentration should be performed regularly (every 4 weeks). A moderate, not clinically significant increase in platelet count has been reported in patients treated with Hemax®. In patients with chronic renal failure, urea, creatinine, potassium, phosphorus and uric acid should be monitored regularly, as slight increases in the values of these parameters have been observed both in dialysis and pre-dialysis patients.
Diet:
Appetite of the patients improves as the haematocrit rises. Therefore, food intake in Hemax®-treated patients tends to increase. Under these circumstances, caution should be taken regarding potassium level, since it may increase because of larger food intake.
Dialysis management:
Therapy with Hemax® results in an increase in haematocrit and a decrease in plasma volume, which could potentially affect dialysis efficiency. Adjustments in dialysis prescription should be made to prevent increasing values of urea, phosphorus, potassium and creatinine. In some cases, increasing the dose of heparin during dialysis may be needed to prevent fistula obstruction.
Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

OVERDOSE:
The maximum dose of Hemax® that can be administered either in bolus or infusion has not yet been determined. Doses of up to 1500 U/kg 3 times per week or up to 60,000 IU/week have been administered to adults without any direct toxic effects. Therapy with Hemax® can result in polyglobulia and patients may experience polyglobulia related symptoms, such as headaches, somnolence, tinnitus, dizziness, etc. In this case, it is advisable to perform a phlebotomy aiming at reducing the haematocrit.
In case of overdose, attend the closest hospital or phone any Toxicology Centre.

PRESENTATIONS:
Lyophilized injectable dosage form
Hemax® 1000 IU/mL, Hemax® 2000 IU/2 mL, Hemax® 3000 IU/2 mL, Hemax® 4000 IU/2 mL, Hemax® 10000 IU/mL, Hemax® 20000 IU/mL, Hemax® 40000 IU/mL.
Packages containing:
1, 3, 6, 10, 12, 24 and 25 vials with lyophilized powder + 1, 3, 6, 10, 12, 24 and 25 ampoules/pre-filled syringe with 1 or 2 mL diluent.

Solution for injection
Hemax® 2000 IU/mL, Hemax® 4000 IU/mL .
Packages containing 1, 5 and 10 vials/pre-filled syringes with 1 mL solution for injection.

STORAGE
Lyophilized injectable dosage form: Store in a fresh dry place, at a temperature below 25 °C.
Solution for injection: Store at 2 °C to 8 °C.

PROTECT FROM EXPOSURE TO DIRECT SUN LIGHT DURING STORAGE. DO NOT FREEZE.
RECONSTITUTE WITH STERILE WATER FOR INJECTION, USP. USE THE RECONSTITUTED SOLUTION IMMEDIATELY.
KEEP OUT OF REACH OF CHILDREN.

Manufactured by: **BIOSIDUS S.A.**
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Medicinal product authorized by the Ministry of Health. Certificate N° 38.777.

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