BIOSIDUS

HEMAX®

Summary of Product Characteristics

NAME OF THE MEDICINAL PRODUCT

Trade Name: HEMAX®
International Non-proprietary Name (INN): Epoetin alpha
Strength: 1000 I.U., 2000 I.U., 3000 I.U., 4000 I.U., 10000 I.U.
Pharmaceutical form: Freeze dried (lyophilized) powder for injection

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial with lyophilized powder contains:

Active ingredient	**HEMAX® 1000 I.U.**	**HEMAX® 2000 I.U.**	**HEMAX® 3000 I.U.**	**HEMAX® 4000 I.U.**	**HEMAX® 10000 I.U.**
Epoetin alpha	1000 I.U.	2000 I.U.	3000 I.U.	4000 I.U.	10000 I.U.

Excipients	**HEMAX® 1000 I.U.**	**HEMAX® 2000 I.U.**	**HEMAX® 3000 I.U.**	**HEMAX® 4000 I.U.**	**HEMAX® 10000 I.U.**
Mannitol	25.0 mg	50.0 mg	50.0 mg	50.0 mg	25.0 mg
Sodium Chloride	3.2 mg	6.4 mg	6.4 mg	6.4 mg	3.2 mg
Monobasic Sodium Phosphate	1.4 mg	2.8 mg	2.8 mg	2.8 mg	1.4 mg
Dibasic Sodium Phosphate Dodecahydrate	4.0 mg	8.0 mg	8.0 mg	8.0 mg	4.0 mg
Human Albumin	2.5 mg	5.0 mg	5.0 mg	5.0 mg	2.5 mg

Each ampoule / pre-filled syringe with diluent contains:

	HEMAX® 1000 I.U.	**HEMAX® 2000 I.U.**	**HEMAX® 3000 I.U.**	**HEMAX® 4000 I.U.**	**HEMAX® 10000 I.U.**
Water for injection	1 mL	2 mL	2 mL	2 mL	1 mL

THERAPEUTICAL ACTION

ATC Code: B03XA01. Antianemic medicine. Erythropoiesis stimulating agent.

INDICATIONS

Hemax® is indicated for:
• **Treatment of anemia in chronic renal failure patients**
Hemax® is indicated in patients on dialysis as well as in patients not requiring dialysis, with the purpose of enhancing and maintaining the red cell level (as evidenced by hematocrit or hemoglobin values) and reducing the need for transfusions. However, patients with asymptomatic anemia not requiring dialysis must have a hemoglobin level below 10 g/dl to be considered apt for the treatment with Hemax®.
Hemax® must no be used as an emergency transfusion substitute in patients requiring immediate correction of severe anemia.
• **Treatment of anemia in zidovudine-treated HIV-infected patients**
Hemax® is indicated for the treatment of anemia in zidovudine-treated HIV-infected patients, with the purpose of enhancing or maintaining the red cell level (as evidenced by the hematocrit or hemoglobin values) and reducing the need for transfusion. It is not indicated for the treatment of anemia related to other factors (iron or folate deficit, hemolysis, gastrointestinal hemorrhage) in this group of patients.
• **Treatment of anemia in cancer patients on chemotherapy**
Hemax® is indicated for the treatment of symptomatic anemia caused by chemotherapy in patients with metastatic 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 to treat anemia related to other factors (iron or folate deficit, hemolysis, gastrointestinal hemorrhage) in this group of patients. Hemax® is not indicated in patients receiving hormone therapy, biological products or radiotherapy without concomitant myelosuppressive chemotherapy.
Hemax® is not indicated in patients on chemotherapy when the anticipated outcome is cure.
• **Reduction of allogenic blood transfusion in surgery patients subjected to programmed surgery.**
Hemax® is indicated in anemic patients (hemoglobin above 10 and ⊠ 13 g/dl), at high risk for perioperative blood loss from elective, non-cardiac, nonvascular surgery to reduce the need for allogenic blood transfusions. It is indicated in patients at high risk for the need of perioperative transfusions with significant, anticipated loss of blood. It is not indicated in anemic patients who will undergo autologous blood donation.
• **Treatment of anemia in premature infants**
Hemax® is indicated for the treatment of anemia in preterm infants with a birth weight between 750 -1,500 g and gestational age under 34 weeks.

CLINICAL PHARMACOLOGY

A) Mechanism of action:
Erythropoietin induces erythropoiesis by stimulating the division and differentiation of erythroid progenitors in the bone marrow, causing the enhancement of the erythrocyte volume and, and therefore, the hematocrit. 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 concentration of erythropoietin increases up to 100 and 1,000 times. This event is also observed in anemia patients.
B) Pharmacokinetics:
Hemax® active ingredient, Epoetin alfa is administered by parentheral route (subcutaneous or intravenous).
The initial increase in reticulocyte count occurs within 7 to 10 days after its administration.

Red cell count, hematocrit and hemoglobin levels increase significantly generally within 2 to 6 weeks after Epoetin alfa administration. The range and extent of the response will depend on the dose and availability of iron reserve. Maximum plasma concentration is achieved after 15 minutes of the intravenous administration of a single dose and between 5 and 24 hours after the subcutaneous administration of such single dose. In the latter case, peak concentrations may remain for 12 to 16 hours and present detectable amounts during at least 24 hours after administration.
Epoetin alfa half-life is 4 to 13 hours post 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. After subcutaneous administration of Epoetin, maximum concentration is observed between 5 and 24 hours after administration and its decline is slower.
In studies performed in adult healthy volunteers, it was observed that half-life after endovenous administration is 20% lower than in patients with renal failure. In a study performed in healthy volunteers, it was observed that the half-life of Hemax® administered by subcutaneous route was 20,8 ± 6,3 hours.
Once treatment is interrupted, hematocrit may start decreasing after 2 weeks.

INDICATIONS AND USAGE

A) Treatment of anemia associated to chronic renal failure:
Chronic renal failure is a clinical condition manifested through a progressive and irreversible decrease of renal function. The treatment with Epoetin has proved to stimulate erythropoiesis in patients with anemia and renal failure, both requiring and not requiring dialysis. The first evidence of erythropoiesis stimulation is the increase of reticulocytes 8 days after the initiation of treatment; subsequently, during the 2nd and 6th weeks the increase of hemoglobin and hematocrit is observed. Velocity and magnitude of such increase depend on the initial dose of Epoetin alfa, hematocrit and hemoglobin basal levels, iron reserve and clinical events that may cause treatment resistance (inflammatory, infection conditions, etc.).
Before starting the treatment with Hemax® other causes of anemia must be discarded (e.g., folic acid or vitamin B12) and concomitant factors that may worsen the anemia must be corrected, especially iron deficiency. Therefore, iron metabolism including ferremia, total iron – binding capacity and percent saturation of transferrin should be evaluated, as well as serum ferritin. It is recommended that patients have transferrin saturation levels above 20 % and ferritin above 100 ng/dL before starting the treatment with Hemax®. Iron levels must be monitored and kept within appropriate during Epoetin treatment.
Blood pressure must be controlled before treatment and strictly monitored during treatment.
Recommended initial dose in adult patients on hemodialysis is 50 IU/Kg/dose by IV route or 40 IU/Kg/dose by SC route, TIW. After four weeks of treatment, the dose must be modified according to the increase achieved in hemoglobin levels:
a) If increase is 1 g/dl or above: continue with the same dose.
b) If increase is below 1 g/dl: increase the dose, by 25 IU/Kg/dose.
The maximum suggested dose is 300 IU/Kg TIW.
Once the target value is achieved, the dose may be reduced by 30% and administration may be changed to SC route if the patient had started treatment by IV route. Maintenance dose must be individualized for each patient. Ten percent of patients under dialysis require a dose of 25 IU/Kg/dose TIW, another 10% require 200 IU/Kg/dose TIW; the average maintenance dose is 75 IU/Kg/dose TIW.
Dose adjustment must be performed at intervals not shorter than 4 weeks, since the response to dose change is evidenced after 2 to 6 weeks.
Renal failure patients not requiring dialysis respond to treatment in the same manner as those not requiring dialysis. Recommended doses are between 75 and 100 IU/Kg/week; and SC route is recommended.
For pediatric patients, the initial recommended dose is the same as for adults. Maintenance dose depends on body weight. Doses usually used, administered three times a week, are: a) weight under 10 kg: 75 to150 IU/Kg/dose; b) weight between 10 and 30 kg: 60 to 150 IU/Kg/dose; c) weight above 30 kg: 30 to 100 IU/Kg/dose. The dose must be reduced gradually until reaching the lowest acceptable level that will keep the target hematocrit and hemoglobin levels.
B) Zidovudine-treated HIV-infected patients:
Hemax® reduces transfusion requirements and increases hematocrit level in zidovudine-treated HIV-infected patients, resulting in a significant improvement in the quality of life. Patients with endogenous erythropoietin levels below 500 mU/ml respond better to treatment; therefore, it is advisable to evaluate endogen erythropoietin before treatment. The recommended initial dose is 100 IU/Kg/dose for adult patients and 150 IU/Kg/dose for pediatric patients, TIW by IV or SC route 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 TIW.
Response to treatment with Epoetin alfa may decrease in case of infectious or inflammatory conditions.
Hemax® administration may be interrupted if hematocrit levels are above 40%, until such level achieves 36%. Dose must be reduced by 25% when treatment is resumed and then, evaluate if hematocrit is maintained within expected values.
C) Anemia in cancer patients on chemotherapy:
In this population, Epoetin increases hematocrit and reduces the need of blood transfusions between the 1st and 4th month of treatment.
Two schemes of Hemax® administration may be applied:
a) Administration three times a week: the recommended initial dose is 150 IU/Kg/dose TIW by SC route. If no response is obtained after 8 weeks, dose can be increased to 50 U/Kg/dose each time up to a maximum of 300 U/Kg/dose TIW. If hemoglobin level reaches 12 g/dl or increases more than 1 g/dl within 2 weeks, the dose must be reduced by 25%.
If hematocrit is above 40%, administration may be interrupted until such value reaches 36%. The dose must be reduced by 25% when treatment is resumed and then evaluate if hematocrit levels are maintained within the expected values.
For pediatric patients between 6 months and 18 years of age, the reported doses were 25 to 300 IU/Kg by SC or IV routes TIW.
b) Administration of single weekly dose: the initial dose in adult patients is 40,000 IU by SC route, once a week. Hemax® should be increased to 60,000 IU if after 4 weeks the hemoglobin level did not increase 1g /dl, free of transfusion. If treatment with Hemax triggers a rapid response, e. g. hemoglobin increase above 1 g/dl in a 2-week period, the dose must be reduced by 25%.
Hemax® administration must be interrupted if hemoglobin value is above 13 g/dl; treatment must be resumed with a 25%reduced dose once hemoglobin has fallen below 12 g/dl. Treatment should be suspended for approximately 4 weeks after chemotherapy.
If patients fail to respond satisfactorily to the initial dose of 60,000 IU after 4 weeks of treatment, they are unlikely to respond to higher doses of Hemax®.
For pediatric patients, weekly doses of 10,000 to 20,000 IU have been applied.
D) Autologous blood transfusion:
In patients with programmed surgery (hip, knee, etc.) on autologous blood transfusion program, it was shown that the administration of Epoetin alfa allows the reduction of the need of allogenic transfusions. The principal predictive response variable to treatment is the hemoglobin level previous to surgery; patients with levels between 10 and 13 g/dl are most benefited with this therapy. The initial dose is 300 IU/Kg/day by SC route, beginning 10 days before surgery and continuing 4 days after surgery. As an alternative scheme, single weekly doses at 600 IU/Kg by SC route may be administered on days 21, 14 and 7 previous to surgery and the fourth dose on the day of surgery.
All patients must receive appropriate iron supplement which must be administered at most when Hemax® therapy initiates and must be continued throughout treatment.
E) Anemia in prematurity:
In the treatment of anemia in premature infants, the use of Hemax® reduces transfusion requirements measured according to both the number of transfused patients and the volume of transfused blood.
The recommended dose is 250 IU/Kg TIW by SC route, from the second week of birth and for 8 weeks.

CONTRAINDICATIONS

Hemax® is contraindicated in patients with:
1. Uncontrolled hypertension
2. Pure red cell aplasia after previous treatment with Epoetin
3. Known hypersensitivity to human albumin.
4. Known hypersensitivity to mammalian cell-derived products

ADVERSE REACTIONS

Chronic renal failure patients:
a) Hypertension: More than 80% of the patients on dialysis have a history of hypertension. Upon Epoetin alfa treatment initiation, hypertension must be controlled and hypertensive treatments as well as food intake restrictions must be corrected accordingly. Twenty five percent of patients receiving Epoetin alfa may develop hypertension and consequently, adjustments in antihypertensive therapy must be made. There is a probable relationship between the velocity of hematocrit rise and the exacerbation of blood pressure. Therefore, it is recommended to reduce the dose of Hemax® if hematocrit increases more than 4 points during a period of 2 weeks.
b) Pure red cell aplasia: Since Epoetin alfa is a protein, some patients may develop anti erythropoietin (Hemax®) antibodies. Some cases of pure red cell aplasia have been associated to neutralizing antibodies against products containing Epoetin alfa. All patients were renal failure patients and received de drug subcutaneously. Such patients cannot receive Hemax® or any other product containing Epoetin.
c) Thrombotic events: An increase of thrombotic events has occurred in dialysis patients with cardiovascular disease receiving Epoetin alfa. Such events included vascular access thrombosis, myocardial acute infarction and others. Thrombotic events were observed in patients assigned to reach hematocrit values above 40 %.

Moreover, this group showed higher mortality rates.
During dialysis, patients may require heparin dose adjustment to prevent venous access thrombosis.
Hemoglobin 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 adult patients under dialysis had seizures, generally associated to hypertension crisis. Blood pressure must be strictly monitored before and during treatment. Epoetin alfa must be administered cautiously in patients with history of seizures.
Zidovudine-treated HIV-infected patients:
Unlike renal failure patients, this group has not reported exacerbation of hypertension, seizures or any other thrombotic events.
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 hemoglobin 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 albumin-related viral disease transmission have been reported.

The following table lists the adverse reactions that usually require medical care:

BASE CONDITION	INCIDENCE	ADVERSE REACTIONS
Chronic Renal Failure	Frequent	Arterial hypertension, headaches, oedema, low back pain, polycytemia, thrombotic complications, fever, hyperkalemia, breathing difficulties, tachycardia, seizures, arthralgias.
	Less frequent	Skin rash, urticaria, peritonitis. Pure red cell aplasia.
Cancer on chemotherapy	Frequent	Oedema, fever.
Zidovudine-treated HIV infection	Frequent	Fever, headaches, skin rash, urticaria.
	Less frequent	Seizures.
Elected surgery	Frequent	Deep venous thrombosis, oedema, fever, headaches, arterial hypertension, skin rash, urticaria, urinary tract infection.

The table that follows details the adverse reactions requiring medical care only to the extent they are sustained over time or hinder daily activity.

BASE CONDITION	ADVERSE REACTIONS
Chronic Renal Failure	Skin reaction (administration site), arthralgia, asthenia, influenza-like syndrome, myalgias, constipation, peritonitis.
Cancer on chemotherapy	Diarrhoea, nauseas, vomiting (very frequent), asthenia, fatigue, paresthesias.
Zidovudine-treated HIV infection	Skin reaction (administration site), asthenia, fatigue, paresthesias.
Scheduled surgery	Skin reaction (administration site), urticaria, anxiety, constipation, dyspepsia, insomnia.
Anaemia of prematurity	Thrombocytosis (platelet count > 500 x 10^9/L)

WARNINGS

Renal failure
In two clinical trials, patients experimented higher risk of mortality and serious cardiovascular events when administered erythropoiesis stimulating agents, trying to reach higher levels of hemoglobin compared to lower levels (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 hemoglobin levels within the range 10 to 12 g/dl.
Cancer patients
The use of erythropoiesis stimulating agents reduced the overall survival and/or increased the risk of tumor progression or recurrence in clinical studies in breast, head and neck, lymphoid, lung (non-small cell) and cervical cancer patients.
To decrease the risks, as well as the risk of serious cardiovascular events, it is recommended to use the lowest dose to avoid blood transfusions. With the purpose of minimizing the risks mentioned above, the hemoglobin levels must not exceed 12 g/dl.
It is recommended to use Hemax® only for the treatment of anemia associated to concomitant myelosuppressive chemotherapy and to discontinue its use after completing the chemotherapy cycle.

The use of erythropoietin is not recommended in patients on chemotherapy when the anticipated outcome is cure.

Patients who received erythropoiesis stimulating agents previously to a surgery to reduce the number of allogenic blood transfusions
A higher incidence of deep venous thrombosis has been reported in patients who received erythropoiesis stimulating agents without prophylactic anticoagulation. Prophylactic anticoagulation must be considered when erythropoiesis stimulating agent is indicated to reduce the number of allogenic transfusions.

PRECAUTIONS

Immunogenicity
Just like for any product administered by parentheral route, precaution must be exercised in case allergic reactions occur after the administration of Hemax®. In clinical trials, minor and transient allergic reactions have been reported. No serious anaphylactic or allergic reactions have been observed due to the use of Epoetin alfa.
Hematology: Exacerbation of porphyria has been observed in Epoetin-treated patients on dialysis. Although this event is not frequently observed, it must be considered in patients with history of porphyria.
Lack or loss of response: The following causes should be discarded when patients receiving maintenance dose fail to respond or to maintain a response to Epoetin alfa: 1. Iron deficiency, 2. Underlying infectious, inflammatory processes or neoplasia, 3. Occult blood loss, 4. Underlying hematologic diseases (thalassemia, myelodysplastic disorder, etc.), 5. Hemolysis, 6. Aluminum intoxication, 7. Vitamin deficiencies: vitamin B12 or folic acid, 8. Cystic fibrosis, 9. Pure red cell aplasia
Iron supplement: Iron requirements may increase if already existent iron stores had been used for erythropoiesis and iron supplement may be recommended for some patients. In some patients, oral administration of such supplement may be insufficient and require the administration of iron sacarate by intravenous route.
Drug interactions: No evidence of interactions between HEMAX® and other drugs has been observed.
Carcinogenesis and mutagenesis: Carcinogenic potential of Hemax® has not been evaluated. Epoetin alfa does not induce bacterial gene mutations or chromosomal aberrations in mammalian cells.
Fertility: A trend for slightly increased fetal wastage was observed in rats treated with Epoetin alfa at 100 to 500 IU/kg intravenously.
Pregnancy: – FDA Category C
There are no sufficient studies on the use of HEMAX® in pregnancy; therefore, this product can only be used when the potential benefit justifies the risk for the fetus. Studies performed in pregnant rats, increase in fetal wastage was observed. In rabbits treated with doses of 500 IU/Kg, no adverse effect was observed.
Breast feeding: 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. Because many drugs are excreted in human milk, caution must be exercised when HEMAX® is administered to nursing mothers.
Pediatric use: Although multiple studies have been performed in newborn babies, nursing infants and older children and have demonstrated that HEMAX® is safe for the prevention and treatment of anemia, the long-term safety of this product has not been established yet.
Laboratory tests: After treatment initiation, hemoglobin or hematocrit must be determined twice a week until it has reached the target range (10 to 12 g/dl, or 30 to 36 %, respectively). Once this range has been achieved, weekly determinations must be performed, during four weeks, to determine in order to check it remains stable. Afterwards, determination will be performed at regular intervals. Platelet count, complete blood count and determination of hemoglobin concentration must be performed regularly (every 4 weeks). Mild increase of platelet counts although not clinically significant have been registered in HEMAX®-treated patients. Serum urea, creatinine, potassium, phosphorus and uric acid should be determined regularly in patients with chronic renal failure, since mild increases have been observed in these parameters both in patients on dialysis and pre-dialysis.
Diet: As the hematocrit increases, there is an improved sense of appetite. For this reason, food ingestion in patients treated with Hemax® usually increases. Under these circumstances, caution must be exercised regarding the potassium level, since it may increase as a consequence of larger food intake.
Dialysis management: Treatment with HEMAX® results in an increase in hematocrit and a decrease in plasma volume that may affect dialysis efficacy. Adjustments in dialysis should be performed in order to avoid the increase in urea, phosphorus, potassium and creatinine levels.
In some cases, it might be necessary to increase the heparin dose during dialysis to avoid fistula obstruction.

OVERDOSAGE

The maximum dose of Hemax® that can be administered in single dose or infusion has not been determined. Doses of up to 1,500 U/Kg TIW or up to 60,000 IU/weekly have been administered to adult patients without any direct toxic effects. The treatment with Hemax® can result in polycythemia and patients may refer related symptoms such as headache, somnolence, tinnitus, dizziness, etc. In this case, it is advisable to perform phlebotomy to decrease the hematocrit. In the event of overdosage, attend to the closest hospital or contact any toxicology center.

HOW SUPPLIED

Freeze-dried powder for injection.
HEMAX® 1000 IU/ml, HEMAX® 10000 IU/ml, HEMAX® 20000 IU/ml, HEMAX® 40000 IU/ml.
Packs containing: 1 vial with freeze dried powder, 1 ampoule containing 1 ml water for injection, 1 disposable syringe, 2 disposable needles and 1 insert.
HEMAX® 2000 IU/2 ml, HEMAX® 3000 IU/2 ml, HEMAX® 4000 IU/2 ml
Packs containing: 1 vial with freeze dried powder, 1 ampoule containing 2 ml water for injection, 1 disposable syringe, 2 disposable needles and 1 insert.

STORAGE CONDITIONS

Freeze dried powder for injection: store in a fresh and dry place at 25°C or under.
Solution for injection: store between 2°C and 8°C.

AVOID DIRECT SUNLIGHT DURING STORAGE. DO NOT FREEZE.
RECONSTITUTE IN WATER FOR INJECTION, USP. ONCE RECONSTITUTED, SOLUTION MUST BE USED IMMEDIATELY.
KEEP OUT OF REACH OF CHILDREN.

Manufacturer: **BIOSIDUS S.A.**, Constitución 4234, C1254ABX, Buenos Aires, Argentina
Technical Direction: Pharm. Paula Olcese,
Medicine authorized by the Health Ministry. Certificate No.: 38.777.

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