380 x 240 mm

BIOSIDUS

HEMAX®

Summary of Product Characteristics

1. 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

2. 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	2.8mg	2.8mg	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	2.5mg

Each apoulle / 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

3. PHARMACEUTICAL FORM: Freeze dried (lyophilized) powder for injection White, homogenous, compact powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications: Hemax® is indicated for:
• *Treatment of anaemia of chronic renal failure (CRF) patients.*
Hemax® is indicated in adult and pediatric patients on dialysis (end-stage renal failure) as well as in those not requiring dialysis, to enhance or maintain the red cell level (as evidenced by the hematocrit or haemoglobin determinations) and to reduce the need for transfusions. Hemax® should not be administered as an emergency transfusion substitute in patients requiring immediate correction of a severe anaemia.
• *Treatment of anaemia in HIV-infected patients zidovudine-induced anemia*
Hemax® is indicated for the treatment of anaemia associated with zidovudine therapy of HIV-infected patients to increase or maintain the red blood cell level [as evidenced by hematocrit or haemoglobin values] and to reduce the need for red blood cell transfusions. It is not indicated for the treatment of HIV-infected patients with anaemia of other aetiology (iron or folate deficit, haemolysis, gastrointestinal haemorrhage).
• *Treatment of anaemia in cancer patients on chemotherapy-induced anemia*
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 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.
Hemax® is not indicated for patients receiving chemotherapy when the anticipated outcome is cure.
• *Reduction of allogeneic blood transfusion in anaemic patients who undergo elective surgery.*
Hemax® is indicated in anaemic patients (haemoglobin between 10 and 13 g/dl) at high risk for perioperative blood loss from elective, 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. Hemax® is not indicated anaemic patients who are willing to donate autologous blood.
• *Treatment of anaemia in premature infants*
Hemax® is indicated for the treatment of anaemia in preterm infants with a body weight between 750 and 1,500 g at birth and a gestational age under 34 weeks.

4.2 Posology and method of administration
A) Treatment of anaemia of chronic renal failure patients.
Arterial tension should be controlled before treatment and strictly monitored under it.
The recommended initial dose in adult anemia associated with chronic renal failure patients is 50-100 IU/Kg by intravenous (IV) or subcutaneous (SC) routes, three times a week (TIW). 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: the dosage of epoetin alpha may be increased by approximately 25%.
Once the target value has been achieved, the dose can be reduced by 30% and administration may be by SC route if the patient had started IV treatment. The maintenance dose must be individualised for each patient. Ten per cent of patients under dialysis require 25 IU/Kg or less 3 times weekly and another 10% requires 200 IU/Kg 3 times weekly; the average maintenance dose is 75 IU/Kg 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.
In paediatric patients, the recommended initial dose is the same as that for adults. The maintenance dose will depend on body weight. The usually applied doses, 3 times weekly, are:
a) body weight below 10 kg: 75 to 150 IU/Kg; b) body weight between 10 and 30 kg: 60 to 150 IU/Kg; c) body weight above 30 kg: 30 to 100 IU/Kg. The dose should be gradually reduced up to the lowest acceptable level that will keep the target hematocrit and haemoglobin levels.
B) Treatment of anaemia in HIV-infected patients zidovudine-induced anemia.
Hemax® reduces transfusion requirements and increases haematocrit level in zidovudine- associated anemia in 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 3 times weekly IV or SC for 8 weeks. Response can be assessed after 8 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 epoetin treatment may decrease in case of infectious or inflammatory conditions.
C) Treatment of anaemia in cancer patients on chemotherapy.
In this population, epoetin increases hematocrit and decreases transfusion requirements between the 1st and 4th month of treatment.
Two Hemax® administration schedules can be applied:
a) TIW administration: The recommended initial dose is 150 U/Kg/dose three times a week SC. If there is no response after 4 weeks, the dose can be increased by 50 U/Kg/dose each time up to a maximum of 300 U/Kg 3 times weekly. If haemoglobin level reaches 12 g/dl or if it increases more than 1 g/dl within 2 weeks, the dose must be reduced by 25%.
If hematocrit is above 40%, administration 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 hematocrit level.
In paediatric patients aged 6 months to 18 years old, reported doses were 25 to 300 IU/kg IV or SC three to seven times a week.
b) Single weekly administration: Initial dose for adults is 40,000 IU, SC, once a week. If haemoglobin did not increase 1 g/dl in 4 weeks –free of transfusions, Hemax® dose should be increased to 60,000 IU. If Hemax treatment triggers a rapid response, e.g., haemoglobin increase above 1 g/dl in 2 weeks, the dose should be reduced by 25%.
D) Reduction of allogeneic blood transfusion in surgery patients
In patients scheduled for elective surgery (orthopedic and cardiac) on autologous transfusion program, epoetin alpha administration reduces the risk of allogeneic transfusions. 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 150-300 IU/Kg/day SC, beginning 10 days before surgery and continuing up to 4 days after it. As an alternative, unique weekly doses at 600 IU/Kg SC, 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 at most when Hemax® treatment has been initiated and should be continued through the epoetin treatment course.
E) Anaemia of prematurity
Subcutaneous dose of 250 IU/kg 3 times, a week, the treatment should be started as soon as possible and it should last 6 weeks.

4.3 Contraindications
HEMAX® is contraindicated in patients with:
1- Uncontrolled arterial hypertension 2- Epoetin-related pure red cell aplasia 3- Known hypersensitivity to human albumin 4- Known hypersensitivity to products derived from mammalian cells.

4.4 Special warnings and precautions for use
Chronic renal failure patients:
Increased risk of mortality and of occurrence of serious cardiovascular events was observed in two clinical studies when erythropoiesis stimulating agents were administered to patients targeted to attain higher haemoglobin levels compared to lower 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.
Cancer diagnosed patients:
Erythropoiesis-stimulating agents (ESAs) shortened overall survival and/or increased the risk of tumour progression or recurrence in some clinical studies in patients with breast, head and neck, lymphoid, non-small cell lung, and cervical cancers.
To decrease these risks, as well as the risk of serious cardiovascular events, it is recommended to use the lowest dose needed to avoid red blood cell transfusion. To minimize the risks above, the haemoglobin level should not be over 12 g/dl.
Use of epoetin is not recommended in patients on chemotherapy when the anticipated outcome is cure.
Patients who receive erythropoiesis stimulating agents peri-surgically to reduce the need of allogeneic red blood cell transfusions:
An increased rate of deep venous thrombosis has been reported for patients on erythropoiesis stimulating agents not receiving prophylactic anticoagulation. Prophylactic anticoagulation should be considered when an erythropoiesis stimulating agent (including epoetin) is indicated to reduce the number of allogeneic transfusions.

PRECAUTIONS:
Immunogenicity: The parenteral administration of any biologic product, including Hemax®, should be attended by appropriate precautions in case allergic cases occur after administration
Haematology: Exacerbation of porphyria has been observed in epoetin-treated patients on dialysis. Although this event is not frequently observed, it should be regarded in patients with history of porphyria
Lack or loss of response: If patients fail to respond or to maintain the response to epoetin maintenance doses, the following causes should be considered and evaluated: 1. Iron deficiency 2. Underlying Infections or inflammatory processes or neoplasia. 3. Occult blood loss 4. Underlying haematologic diseases (thalasaemia, myelodysplasia, etc.) 5. Haemolysis 6. Aluminum overload 7. Vitamin deficiencies: vitamin B12 or folic acid 8. Cystic fibrosis 9. Pure red cell aplasia 10. Bone marrow fibrosis 11. Bone marrow suppression from uremia 12. Hyperparathyroidism/osteitis fibrosa cystica 13. Erythrocyte enzyme abnormalities
Iron supplement: Iron requirements may increase if already existent iron stores had been used for erythropoiesis. Some physicians recommend iron supplement for those patients whose iron stores are not enough due to frequent transfusions. In some patients, oral administration of such supplement may be insufficient and require parenteral iron (such as iron sucrose) by intravenous route.
Diet: When hematocrit increases, there is an improved sense of appetite. It is for this reason that food ingestion in Hemax®-treated patients tends to increase. Under these circumstances, caution should be taken regarding potassium level, since it may increase as a consequence of larger food intake.
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 disease have been identified for the albumin used in Hemax®.

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4.5 Interactions with other medicinal products
Antihypertensive agents: Epoetin may increase blood pressure, possibly to hypertensive levels, especially when the hematocrit is rising rapidly; more intensive antihypertensive therapy [increase in dosage, administration of additional and/or more potent medications] may be required to control blood pressure
Heparin: An increase in heparin dosage may be required in patients receiving hemodialysis, because epoetin-induced increases in red blood cell volume may lead to blood clotting in the dialyzer and/or vascular access [arteriovenous shunt]
Iron supplements: Iron requirement may be increased as existing iron stores are used for erythropoiesis; some clinicians recommend supplementation for all patients who are not overloaded with iron because of frequent blood transfusions; in some patients, oral iron supplementation may be insufficient and intravenous iron dextran may be required.

4.6 Pregnancy and lactation
Carcinogenesis and mutagenesis
Carcinogenetic potential of HEMAX® has not been evaluated. Epoetin does not induce bacterial gene mutations or chromosomal aberrations in mammalian cells.
Pregnancy Category C: There are no sufficient 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. In pregnant rats, increase of foetal loss was observed. Epoetin alpha should be used during pregnancy only when the potential benefits justify the possible risks to the foetus.
Nursing mothers: 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.

4.7 Effects on the ability to drive and use machines
No data are available.

4.8 Undesirable effects
Chronic renal failure patients:
A) Arterial hypertension: More than 80% of hemodialysis patients have a history of arterial hypertension. Arterial tension should be strictly controlled when epoetin alpha treatment is initiated and antihypertensive treatments as well as food intake restrictions should be corrected accordingly. It has been reported that approximately 25% of patients on dialysis treated with epoetin alpha may develop hypertension and consequently, adjustments in antihypertensive therapy should be made.
There is an eventual relationship between the velocity of hematocrit rise and the exacerbation of arterial tension. Therefore, a decrease of Hemax® dose is recommended if hematocrit increases more than 4 points during a 2-week period.
B) Pure red cell aplasia: Since epoetin alpha 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 alpha containing products. This has been reported in patients with renal failure who received the drug by subcutaneous route. These patients shall not receive Hemax® or any other epoetin containing product.
C) Thrombotic events: An increase of thrombotic events has occurred in dialysis patients with cardiovascular disease receiving epoetin alpha. These included vascular access thrombosis, myocardial acute infarction and others. Thrombotic events were observed in patients assigned to reach a target hematocrit >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 alpha, approximately 5% of adult patients on dialysis had seizures generally associated with arterial hypertension crisis. Arterial tension should be closely monitored before and during treatment. Caution should be taken when administering epoetin alpha to patients with history of seizures.
Zidovudine-treated HIV-infected patients:
Differently from renal failure patients, no exacerbation of arterial hypertension, seizures or thrombotic events have been reported for this group of patients.
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 alpha 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 disease have been identified for albumin.

The table that follows details the adverse reactions requiring 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.

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

Paediatric 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 anaemia, the long-term safety of this product has not been established yet.

4.9 Overdose
The maximum amount of Hemax® that can be safely administered in a single dose or through infusion has not been determined yet. Doses of up to 1500 U/Kg TIW 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.

5. CLINICAL PHARMACOLOGY
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: ATC B03XA01
Mechanism of Action: 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 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 erythropoietin concentration increases up to 100- and 1000-fold. This is also observed in anaemic patients.

5.2 Pharmacokinetic properties
Epoetin alpha, Hemax® active ingredient, is indicated for parenteral (subcutaneous or intravenous) administration. The initial enhancement in the reticulocyte count occurs within 7 to 10 days following administration.
Red cell count, hematocrit and haemoglobin levels increase significantly generally within 2 to 6 weeks following epoetin alpha administration. The range and extent of the response will depend on the dose and availability of iron stores.
The maximum plasma concentration is achieved 15 minutes following the administration of a unique intravenous dose and between 5 to 24 hours following subcutaneous administration as a single dose. Peak concentrations following sc administration may remain for 12 to 16 hours and detectable amounts can be observed for at least 24 hours following administration.
Epoetin alpha 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. Following epoetin subcutaneous administration, the maximum concentration is observed between 5 to 24 hours post administration and its decline is slower.
In adult healthy volunteers, half-life following intravenous administration was 20% lower than in patients with renal failure. In a trial that involved healthy volunteers, Hemax® half-life, administered by sc route, was 20.8 ± 6.3 hours.
Once the treatment is withdrawn, hematocrit may start decreasing after 2 weeks.

5.3 Preclinical safety data
Carcinogenesis and mutagenesis: Carcinogenic potential of Hemax® has not been evaluated. Epoetin does not induce bacterial gene mutations or chromosomal aberrations in mammalian cells.
Fertility: In female rats treated with epoetin at 100 to 500 IU/kg intravenously, there was a trend for slightly increased foetal wastage.

6. PHARMACEUTICAL PARTICULARS
6.1 List of Excipients : Human Serum Albumin, Mannitol, Sodium chloride, Monosodium phosphate, Disodium Phosphate Dodecahydrated, Water for Injection.
6.2 Incompatibilities : In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products.
6.3 Shelf life : HEMAX 2000 I.U. has shown to be stable in its pharmaceutical form during 24 months.
6.4 Special Precautions for storage : HEMAX® should be stored in a fresh and dry place, below 30°C.
6.5 Nature and contents of container : HEMAX® containing epoetin alpha is available in type I-glass vials, containing colour coded labels and caps.
6.6 Instruction for use, handling and disposal : Patients should be instructed in the use of aseptic techniques when administering HEMAX®.
It should not be used and should be discarded if: 1. The solution is not limpid, contains suspended particles or sediments. 2. It may have been frozen.
Any waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER
BIOSIDUS S.A.
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8. MARKETING AUTHORIZATION NUMBER
Certificate Number: 38,777

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