HEMAX®

هيميكس®

BIOSIDUS

[RECOMBINANT HUMAN ERYTHROPOIETIN]

Injection: 2000 IU, 4000 IU, 1000 IU

DESCRIPTION:
HEMAX® is a product that contains epoetin alfa (recombinant human Erythropoietin, r-HuEPO) as active ingredient. Epoetin is a 165-amino acid glycoprotein manufactured by recombinant DNA technology, obtained from a genetically engineered mammalian cell line. Epoetin has a maximum purity level and it is indistinguishable from the natural human erythropoietin.

COMPOSITION:
Each vial with lyophilized powder contains:

Active ingredient:
HEMAX® 2000 I.U.: Recombinant Human Erythropoietin 2000 I.U.
HEMAX® 4000 I.U.: Recombinant Human Erythropoietin 4000 I.U.
HEMAX® 10000 I.U.: Recombinant Human Erythropoietin 10000 I.U.

Excipients:

HEMAX® 2000 I.U.** Mannitol 50 mg, Sodium Chloride 6.4 mg, Monosodium Phosphate 2.8 mg, Disodium Phosphate Dodecahydrated 8 mg, Human Albumin 5 mg.

HEMAX® 4000 I.U.** Mannitol 50 mg, Sodium Chloride 6.4 mg, Monosodium Phosphate 2.8 mg, Disodium Phosphate Dodecahydrated 8 mg, Human Albumin 5 mg.

HEMAX® 10000 I.U.* Mannitol 25 mg, Sodium Chloride 3.2 mg, Monosodium Phosphate 1.4 mg, Disodium Phosphate Dodecahydrated 4 mg, Human Albumin 2.5 mg.
*each solvent ampoule contains: water for injection 1 mL.
**each solvent ampoule contains: water for injection 2 mL.

THERAPEUTIC ACTION:
ATC Code: B03XA01. Antianaemic medicine. Erythropoiesis stimulating agent.

INDICATIONS:
HEMAX® is indicated for:
A) 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 haematocrit or haemoglobin determinations) and to reduce the need for transfusions. However, patients with symptomatic anaemia not requiring dialysis should have a haemoglobin level below 10 g/dL to be considered apt for **HEMAX®** treatment. **HEMAX®** should not be administered as an emergency transfusion substitute in patients requiring immediate correction of a severe anaemia.
B) Treatment of anaemia in Zidovudine-treated HIV-infected patients. **HEMAX®** is indicated for the treatment of anaemia associated with zidovudine-treated HIV-infected patients to increase or maintain the red blood cell level [as evidenced by haematocrit or haemoglobin values] and to reduce the need for transfusions. It is not indicated for the treatment of HIV-infected patients with anaemia of other aetiology (iron or folate deficit, hemolysis, gastrointestinal haemorrhage).
C) Treatment of anaemia in cancer patients on chemotherapy. **HEMAX®** is indicated for the treatment of symptomatic anaemia caused by chemotherapy in patients with metastasic 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, hemolysis, gastrointestinal haemorrhage) 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 for patients receiving chemotherapy when the anticipated outcome is cure.**
D) 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, noncardiac, 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.
E) Treatment of anaemia in premature infants: **HEMAX®** is indicated for the treatment of anaemia in preterm infants with a body weight between 750 and 1500 g at birth and a 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 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.
B) Pharmacokinetics:
Epoetin alfa, **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, haematocrit and haemoglobin levels increase significantly generally within 2 to 6 weeks following epoetin alfa 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 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. 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, haematocrit may start decreasing after 2 weeks.

THERAPEUTIC USE AND POSOLOGY:
A) Treatment of anaemia secondary to chronic renal failure:
Chronic renal failure is a condition manifested through a progressive and irreversible decrease of renal function. Epoetin treatment has shown to stimulate erythropoiesis in patients with anaemia and renal failure requiring dialysis or not. The first evidence of erythropoiesis stimulation is the increase of reticulocytes 8 days after treatment initiation; afterwards, in the 2nd and 6th weeks, an haemoglobin and haematocrit increase is observed. Velocity and magnitude of such increase depend on the initial dose of epoetin alfa, haematocrit and haemoglobin basal levels, iron stores and those clinical conditions that may trigger treatment resistance (inflammatory or infectious conditions, etc).
Prior to **HEMAX®** therapy, other causes of anaemia should be discarded (e.g., folic acid or vitamin B_{12} deficiency) and concomitant factors that may worsen the anaemia, particularly iron deficiency, should be corrected. Therefore, iron metabolism including ferremia, total iron – binding capacity and percent saturation of transferrin should be evaluated, as well as serum ferritin. In patients, recommendable level for transferrin saturation is above 20 % and for serum ferritin it should be over 100 ng/dL before **HEMAX®** therapy initiation. Iron levels should be monitored and kept within appropriate levels during epoetin treatment.
Arterial tension should be controlled before treatment and strictly monitored under it.
The recommended initial dose in adult patients under hemodialysis is 50 I.U./Kg/dose by intravenous (IV) or 40 I.U./Kg/dose by 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: raise the dose by increments of 25 I.U./Kg/dose.
The suggested maximum dose is 300 I.U./Kg TIW.
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 I.U./Kg/dose TIW and another 10 % require 200 I.U./Kg/dose TIW; the average maintenance dose is 75 I.U./Kg/dose TIW.
Dose adjustments should be performed between intervals not shorter than 4 weeks, since response to dose changes is evidenced after 2 to 6 weeks.
Renal failure patients not requiring dialysis show the same response as those on dialysis. The recommended doses fall between 75 and 100 I.U./Kg/week, and the recommended route of administration is SC.
In pediatric patients, the recommended initial dose is the same as that for adults. The maintenance dose will depend on body weight. The usually applied doses, TIW, are:
a) body weight below 10 kg: 75 to 150 I.U./Kg/dose; b) body weight between 10 and 30 kg: 60 to 150 I.U./Kg/dose; c) body weight above 30 kg: 30 to 100 I.U./Kg/dose. The dose should be gradually reduced up to the lowest acceptable level that will keep the target haematocrit and haemoglobin levels.
B) Zidovudine-treated HIV-infected Patients: 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 below 500 mU/ml respond better to treatment; therefore, it is advisable to evaluate endogen erythropoietin before treatment.
The recommended initial dose is 100 I.U./Kg/dose for adults and 150 I.U./Kg/dose for children TIW IV or SC 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 I.U./Kg increases to a maximum of 300 I.U./Kg TIW.
Response to epoetin treatment may decrease in case of infectious or inflammatory conditions.
If haematocrit levels are above 40 %, **HEMAX®** administration may be interrupted until such level achieves 36 %. The dose must be reduced by 25 % when treatment is re-initiated and thereafter, it should be evaluated if target haematocrit is maintained.
C) Anaemia in cancer patients on chemotherapy: In this population, epoetin increases haematocrit 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 I.U./Kg/dose three times a week SC. If there is no response after 8 weeks, the dose can be increased by 50 I.U./Kg/dose each time up to a maximum of 300 I.U./Kg/dose TIW. 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 haematocrit 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 it should be evaluated if target haematocrit is maintained.
In pediatric patients aged 6 months to 18 years old, reported doses were 25 to 300 I.U./kg IV or SC three to seven times a week.
b) Single weekly administration: Initial dose for adults is 40000 I.U., SC, once a week. If haemoglobin did not increase 1 g/dL in 4 weeks –free of transfusions, **HEMAX®** dose should be increased to 60000 I.U.. 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 %.
Hemax administration should be discontinued if haemoglobin level is above 13 g/dL; treatment re-initiation should be at a 25 % lower dose once haemoglobin has fallen below 12 g/dL. Treatment should be discontinued approximately 4 weeks after chemotherapy.
If patients fail to respond satisfactorily to the 60000 I.U. weekly dose after 4 weeks, they are unlikely to respond to higher **HEMAX®** doses.
In pediatric patients, weekly doses ranging 10000 to 20000 I.U. have been used.
D) Autologous blood transfusions: In patients scheduled for elective surgery (hip, knee, etc.) on autologous transfusion program, it was demonstrated that epoetin alfa 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 300 I.U./Kg/day SC, beginning 10 days before surgery and continuing up to 4 days after it. As an alternative, unique weekly doses at 600 I.U./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: In the anaemia of prematurity, **HEMAX®** administration reduces transfusion requirements measured both according to the number of transfused patients as well as on the volume of transfused blood.
The recommended dose is 250 I.U./Kg TIW, SC, from second week of birth and for eight weeks.

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.

ADVERSE REACTIONS
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 alfa 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 alfa may develop hypertension and consequently, adjustments in antihypertensive therapy should be made.
There is an eventual relationship between the velocity of haematocrit rise and the exacerbation of arterial tension. Therefore, it is recommended to reduce **HEMAX®** dose if haematocrit increases more than 4 points during a 2-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 and 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 alfa. These included vascular access thrombosis, myocardial acute infarction and others. Thrombotic events were observed in patients assigned to reach a target haematocrit of > 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, approximately 2.5 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 alfa 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 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 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, œdema, low back pain, polycythemia, thrombotic complications, fever, hyperkalemia, breathing difficulties, tachycardia, seizures, arthralgias.
	Less frequent	Skin rash, urticaria, peritonitis. Pure red cell aplasia
Cancer on chemotherapy	Frequent	Œdema, fever.
Zidovudine-treated HIV infection	Frequent	Fever, headaches, skin rash, urticaria
	Less frequent	Seizures
Elected surgery	Frequent	Deep venous thrombosis, œdema, 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 interfere daily activity.

BASAL PATHOLOGY	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.
Scheduled surgery	Skin reaction (administration site), urticaria, anxiety, constipation, dyspepsia, insomnia
Anaemia of prematurity	Thrombocytosis (platelet count > 500 x 10^9/L)

WARNINGS:
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 (ESAs) were administered in 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: 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. It is recommended to use **HEMAX®** only for the treatment of anaemia due to concomitant myelosuppressive chemotherapy and to discontinue its use once the chemotherapy cycle has been completed.
Use of erythropoietins is not recommended in patients on chemotherapy when the anticipated outcome is cure.

Patients who received erythropoiesis stimulating agents perisurgically 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 is indicated to reduce the number of allogeneic transfusions.

PRECAUTIONS:
Immunogenicity: The parenteral administration of any biologic product should be attended by appropriate precautions in case allergic reactions occur after **HEMAX®** administration. In clinical trials, minor and transitory allergic reactions have been reported. No serious anaphylactic or allergic reactions have been observed with epoetin use.
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 (thalassemia, myelodysplasia, etc.).
5. Hemolysis.
6. Aluminium 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 have been used for erythropoiesis. Some physicians recommend iron supplement for those patients whose iron stores are insufficient due to frequent transfusions. In some patients, oral administration of such supplement may be insufficient and require saccharated iron by intravenous route.
Drug interactions: No evidence of interaction between **HEMAX®** and other drugs was observed.
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 I.U./kg intravenously, there was a trend for slightly increased foetal wastage.
Pregnancy: FDA C Category. There are no sufficient studies on the use of **HEMAX®** in pregnant women; therefore, this product should be used during pregnancy if and only if potential benefit justifies the risk to the foetus. In studies performed on female rats, increase in foetal wastage was observed. In treated rabbits with 500 I.U./kg, no adverse effect was observed.
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.
Pediatric Use: Although multiple studies have been performed in newborn babies, nursing infants and older children which 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.
Laboratory monitoring: After treatment initiation, haemoglobin and haematocrit should be monitored twice weekly till target value (10 to 12 g/dL, or 30 to 36 %, respectively). Once this value has been achieved, weekly determinations should be taken for 4 weeks in order to verify if it remains steady. Afterwards, determinations will be performed at regular intervals. Platelet counts, as well as red and white cells counts plus haemoglobin determination should be performed regularly (every 4 weeks). Mild increase of platelet counts although not clinically significant have been registered in **HEMAX®**-treated patients. In patients with CRF serum urea, creatinine, potassium, phosphorus and uric acid should be regularly monitored, since mild increases have been observed for these parameters in patients on dialysis as well as in those on pre-dialysis.
Diet: When haematocrit increases, there is an improved sense of appetite. For this reason 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.
Dialysis Management: **HEMAX®** treatment causes an increase in haematocrit and a decrease in plasma volume which could affect dialysis efficacy. Adjustments should be performed in dialysis in order to prevent urea, phosphorus, potassium and creatinine values from increasing.
In some cases, it might be necessary to increase the heparin dose during dialysis to prevent fistula clotting.

OVERDOSAGE:
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 I.U./Kg TIW or up to 60000 I.U./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 overdosage, attend the closest hospital or phone any Toxicology Centre.

HOW SUPPLIED:
HEMAX® 10000 I.U.: Packages with 1 vial of lyophilized powder containing Recombinant Human Erythropoietin 10000 I.U., 1 ampoule with 1 mL of solvent, one disposable syringe and 2 disposable needles.

HEMAX® 2000 I.U. and 4000 I.U.: Packages with 1 vial of lyophilized powder containing Recombinant Human Erythropoietin 2000 I.U. & 4000 I.U., 1 ampoule with 1 mL of solvent, one disposable syringe and 2 disposable needles.

REGISTRATION NUMBER:
HEMAX® 2000 IU: 021935
HEMAX® 4000 IU: 021934
HEMAX® 10,000 IU: 039896

Manufacturing Licence No : 4025/06

- To be sold on prescription of a registered medical practitioner only.
- Keep all medicines out of sight & reach of children.
- Store in fresh and dry place, at 25°C or under.

Manufactured by:
Biosidus S.A.
Av. De los Quilmes 137 (B1883FIB), Bernal, Quilmes, Province of Buenos Aires, Argentina.

Imported by:
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Marketed by:
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Tipu Sultan Road, Off Shahra-e-Faisal, Karachi - Pakistan.

- صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔
- تمام دوائیں بچوں کی نظر اور پہنچ سے دور رکھیں۔
- دوا کو ٹھنڈی اور خشک جگہ پر ۲۵ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

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