1. Name of the medicinal product

HEMAX 4000
(Recombinant Human Erythropoietin 4000 IU/2mL)

2. Qualitative and quantitative composition

Each vial with freeze dried powder contains:
Recombinant human Erythropoietin ... 4000 IU

Each vial with solution contains:
Recombinant human Erythropoietin ... 4000 IU

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Freeze dried powder and injectable solution.

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 paediatric patients on dialysis (end-stage renal failure) as well as in those not requiring dialysis, to enhance or maintain the red cell level (as manifested by the haematocrit or haemoglobin determinations) and to decrease the need for transfusions. However, patients not requiring dialysis should have a haemoglobin level below 10 g/dl to be considered apt for Hemax treatment.

Hemax should not be used as a substitute for emergency transfusion in patients who require immediate correction of severe anaemia.

Treatment of anaemia in zidovudine-treated HIV-infected patients
Hemax is indicated for the treatment of severe anaemia related to therapy with zidovudine in adult or paediatric HIV-infected patients. It is not indicated for the treatment of anaemia in HIV-infected patients due to other factors.

Treatment of anaemia in cancer patients on chemotherapy
Hemax is indicated for the treatment of anaemia in adult and paediatric patients with non-myeloid malignancies where anaemia is due to the effect of concomitantly administered chemotherapy.

Reduction of allogeneic blood transfusions in surgery patients
It is indicated for patients at high risk for perioperative transfusions with significant, anticipated blood loss.

Treatment of anaemia in premature infants

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

4.2 Posology and method of administration

A) Treatment of secondary anaemia 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, a haemoglobin and haematocrit increase is observed. Speed and magnitude of such increase depend on the epoetin initial dose, 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 B12 deficiency) and concomitant factors that may worsen the anaemia, especially iron deficiency, should be regulated. Therefore, iron metabolism including ferremia, saturation total capacity and transferrin saturation average 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 haemodialysis is 50 IU/Kg/dose IV or 40 IU/Kg/dose SC, TIW. After four weeks under treatment, the dose should be modified regarding haemoglobin level increases:

a) If increase equals 1 g/dl or above: keep the same dose.
b) If increase is below 1 g/dl: raise the dose to 25 IU/Kg/dose.
c) The suggested maximum dose is 300 IU/Kg TIW.
d) Once the target level is achieved, the dose can be reduced 30% and the SC route can be selected if the patient had started IV treatment. The maintenance dose must be individualised for each patient. 10% of patients under dialysis require 25 IU/Kg/dose TIW and another 10% requires 200 IU/Kg/dose TIW; the median maintenance dose is 75 IU/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 who are receiving it. The recommended doses fall between 75 and 100 IU/Kg/week, SC.

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, TIW, are:

a) body weight below 10 kg: 75 to 150 IU/Kg/dose;
b) body weight between 10 and 30 kg: 60 to 150 IU/Kg/dose;
c) body weight above 30 kg: 30 to 100 IU/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, causing a meaningful increase in the quality of life. Patients with endogenous erythropoietin levels below 500 mU/ml show a better response to the treatment; therefore, it is advisable to dose endogenous erythropoietin prior to treatment.

The recommended initial dose is 100 IU/Kg/dose for adults and 150 IU/Kg/dose for children TIW IV or SC for 8 weeks. Response can be assessed after 4 treatment weeks. If no satisfactory response is obtained, this dose can be increased from 50 IU/Kg to a maximum of 300 IU/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, a target haematocrit level should be 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:

Three times a week: The recommended initial dose is 150 IU/Kg/dose three times a week SC. If there is no response after 8 weeks, the dose can be increased in 50 IU/Kg/dose each time up to a maximum of 300 IU/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 25%.

If haematocrit is above 40%, administration can be interrupted until such value reaches 36%. The dose must be reduced 25% when treatment is re-initiated and then a target haematocrit level should be maintained.

In paediatric patients ranging 6 months to 18 years old, reported doses were 25 to 300 IU/kg IV or SC three to seven times a week.

Unique weekly dose: Initial dose for adults is 40,000 IU, SC, once a week. If haemoglobin did not increase 1 g/dl in 4 weeks with no transfusion at all, Hemax dose should be increased to 60,000 IU. If Hemax treatment triggers a fast response, e.g., haemoglobin increase above 1 g/dl in 2 weeks, the dose should be reduced 25%.

Hemax administration must be interrupted if haemoglobin level is above 13 g/dl; treatment re-initiation should regard a dose 25% lower when haemoglobin has fallen below 12 g/dl.

If patients fail to respond satisfactorily to the 60,000-IU weekly dose after 4 weeks, they are unlikely to respond to higher Hemax doses.

In paediatric patients, weekly doses ranging 10,000 to 20,000 IU 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 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 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 at latest when Hemax treatment starts, until its end.

E) Anaemia of prematurity: In the anaemia of prematurity, Hemax administration reduces transfusion requirements based on the number of transfused patients as well as on the volume of transfused blood. The recommended dose is 250 IU/Kg TIW, SC, from second week of birth and for eight weeks.

4.3 Contraindications

Hemax is contraindicated in patients with:

1. Uncontrolled arterial hypertension.
2. Epoetin-associated 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

Immunogenicity: The parenteral administration of any biologic product should be attended by appropriate precautions in case allergic cases 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.

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 not be enough and require saccharated iron by intravenous route.

Carcinogenesis and mutagenesis: Carcinogenic potential of Hemax has not been evaluated. Epoetin does not induce bacterial gene mutations or chromosomal aberrations in mammalian cells.

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.

Laboratory monitoring: After treatment initiation, haemoglobin and haematocrit should be monitored twice weekly till the target rate (10 to 12 g/dl, or 30 to 36%, respectively) is observed. Once this rate 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). Modest platelet increases although not clinically significant have been registered in Hemax-treated patients.

In patients with CRF, serum chemistry values (including urea, creatinine, potassium, phosphorus and uric acid) should be regularly monitored, since moderate increases have been observed in 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. 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 ingestion.

Dialysis management: Hemax treatment causes an increase in the 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.

4.5 Interaction with other medicinal products and other forms of interaction

No evidence of interaction between Hemax and other drugs was observed.

4.6 Fertility, pregnancy and lactation

Fertility: In female rats treated with epoetin at 100 to 500 IU/kg endovenously, there was a trend for slightly increased fetal wastage.

Pregnancy: There are no adequate studies regarding Hemax administration in pregnant women; therefore, this product should be used during pregnancy if and only if potential benefit justifies the risk for the foetus. In studies performed in female rats, increase in fetal wastage was observed. In treated rabbits with 500 IU/kg, no adverse effect was observed.

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 excreted in human milk, caution should be exercised when Hemax is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Given that Hemax can cause somnolence and dizziness as adverse effects, the use of machines and driving of vehicles is not advised during treatment.

4.8 Undesirable effects

Those requiring medical care:

Basal pathology	Incidence	Adverse reactions
Chronic Renal Failure	More frequent	Arterial hypertension, headaches, oedema, low back pain, polycythemia, thrombotic complications, fever, hyperkalaemia, breathing difficulties, tachycardia, seizures, arthralgias.
	Less frequent	Skin rash, urticaria. Pure red cell aplasia.
Cancer on chemotherapy	More frequent	Oedema, fever.
Zidovudine-treated HIV infection	More frequent	Fever, headaches, skin rash, urticaria.
	Less frequent	Seizures.

Scheduled surgery	More frequent	Deep venous thrombosis, oedema, fever, headaches, arterial hypertension, skin rash, urticaria, urinary tract infection.

Those requiring medical attention only if they last longer than they should or interfere with daily activities:

Basal pathology	**Adverse reactions**
(All conditions)	Diarrhoea, nausea, vomiting (very frequent), fatigue.
Chronic Renal Failure	Skin reaction (administration site), arthralgia, asthenia, influenza-like syndrome, myalgias, constipation, peritonitis.
Cancer on chemotherapy	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).

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

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 IU/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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

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 to 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 situation is also observed in anaemic patients.

5.2 Pharmacokinetic properties

Epoetin, 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 meaningfully generally within 2 to 6 weeks following epoetin administration. The range and extension 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 the subcutaneous administration as an only dose. In this last case, peak concentrations may remain for 12 to 16 hours and also detectable amounts can be observed for at least 24 hours following administration.

Epoetin 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 endovenous administration is 20% lower than in patients with renal failure. In a trial that involved healthy volunteers, Hemax half-life, using subcutaneous route, was 20.8 ± 6.3 hours. Once the treatment is withdrawn, haematocrit may start decreasing after 2 weeks.

5.3 Preclinical safety data

Toxicology summary: Biosidus performed a single-dose toxicity study, two repeat-dose toxicity studies (comparative tests) and a comparative safety study between Hemax and Eprex under repeat-dose conditions. The investigators concluded that the product under analysis increased erythropoiesis and did not cause any toxic alterations to fluids and organic tissues of the tested animals (mice).

The comparative study concluded that both products show a similar response pattern, accordingly with the bio-similarity between them.

Genotoxicity and carcinogenicity: Erythropoietin is not considered a genotoxic substance.

Alike the genotoxicity assessment, erythropoietin is not a carcinogen (on the contrary, it can protect against the damage induced by several carcinogens).

6. Pharmaceutical particulars

6.1 List of excipients

Mannitol ... 50.0 mg
Sodium chloride ... 6.4 mg
Sodium phosphate monobasic ... 2.8 mg
Sodium phosphate dibasic dodecahydrate ... 8.0 mg
Human albumin ... 5.0 mg
Water for injection (diluent) ... 2 mL

6.2 Incompatibilities

In the absence of compatibility studies, this product should not be combined with others.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Freeze dried injectable: Store in a fresh and dry place, at 25°C or under.
Injectable solution: Store in the fridge, between 2°C and 8°C.

6.5 Nature and contents of container

Freeze dried injection

HEMAX 4000 IU/2mL: packages containing 1 vial with freeze dried powder, 1 ampoule with diluent 2 mL, 1 disposable syringe, 2 disposable needles and leaflet.

Injectable solution

HEMAX 4000 IU/mL: packages containing 1 and 5 vials with 1 mL of injectable solution.

6.6 Special precautions for disposal and other handling

Avoid direct sunlight during storage. Do not freeze. Reconstitute with sterile water for injection, USP. Once the solution is reconstituted, use immediately. Keep out of reach of children.

7. Marketing authorisation holder

Biosidus S.A.

8. Marketing authorisation number

H2021/CTD8307/18456

9. Date of first authorisation/renewal of the authorisation

3rd September, 2021

10. Date of revision of the text

24th August, 2026