Elea	**Producto:** Pronivel 2000/4000 (Jeringa Prellenada) - **DOSSIER**		**Código:** 000000-00 reemplaza a	
	Material: Prospecto		**Países:** FILIPINAS	
	Fecha: 09/08/22		**Nº Diseño:** 0797/2	
Medidas: 180x280 mm	**Plano:**	**Escala:** 100%	**Especif. Técnicas:** ☐ LACA ☐ CUÑO ☐ BRAILLE	
Nº Colores: 1	**Citocromía** ☐	**Pantones:** ■ Negro U		
NOTAS: ☐ El color representa al troquel. Los elementos representados con este color no deben imprimirse.			**Cód. de barras:** Laetus XXX	
Motivo de emisión: Modifica texto de dirección, incorporamos grafica anterior.				

LOS COLORES QUE SE VEN EN ESTA IMPRESIÓN PUEDEN TENER DESVIACIONES RESPECTO DE LOS COLORES PANTONE ESPECIFICADOS Y NO DEBEN USARSE COMO PATRÓN DE COMPARACIÓN

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Epoetin Alfa
Pronivel®

Rx

2.000 I.U./ml Solution for injection (IV/ SC)
4.000 I.U./ml Solution for injection (IV/ SC)

Hematopoietic Growth Factor

Composition:

Pronivel® 2.000 I.U.: *Each prefilled syringe of 1 mL contains:* Recombinant human erythropoietin alpha (rHuEPO alpha) 2.000 I.U. Excipients: Human serum albumin 2.5 mg; Sodium chloride 5.84 mg; Monohydrate monosodium phosphate 0.827 mg; Anhydrous dibasic sodium phosphate 1.987 mg, Water for injection q.s. to 1.0 mL.

Pronivel® 4.000 I.U.: *Each prefilled syringe of 1 mL contains:* Recombinant human erythropoietin alpha (rHuEPO alpha) 4.000 I.U. Excipients: Human serum albumin 2.5 mg; Sodium chloride 5.84 mg; Monohydrate monosodium phosphate 0.827 mg; Anhydrous dibasic sodium phosphate 1.987 mg, Water for injection q.s. to 1.0 mL.

Therapeutic action:

Anti-anemia hormonal agent. Hematopoietic agent. Erythropoiesis stimulant agent.
ATC B03XA01

Indications:

- Indicated for the Treatment of symptomatic anemia associated with chronic renal failure (CRF):
• In adults and pediatrics aged 1 to 18 years on hemodialysis and adult patients on peritoneal dialysis.
• In adults with renal insufficiency not yet undergoing dialysis for the treatment of severe anemia of renal origin accompanied by clinical symptoms in patients.

- Indicated for the treatment of anemia and reduction of transfusion requirements: In adults receiving chemotherapy for solid tumors, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status (e.g. cardiovascular status, pre-existing anemia at the start of chemotherapy).

- Indicated in adults in a predonation programme to increase the yield of autologous blood.
Treatment should only be given to patients with moderate anemia (hemoglobin concentration range between 10 to 13 g/dl [6.2 to 8.1 mmol/l], no iron deficiency) if blood saving procedures are not available or insufficient when the scheduled major elective surgery requires a large volume of blood (4 or more units of blood for females or 5 or more units for males).

- Indicated for non-iron deficient adults prior to major elective orthopedic surgery having a high perceived risk for transfusion complications to reduce exposure to allogeneic blood transfusions. Use should be restricted to patients with moderate anemia (e.g. hemoglobin concentration range between 10 to 13 g/dl) who do not have an autologous predonation programme avai-lable and with expected moderate blood loss (900 to 1,800 ml).

Pharmacological properties:

- Pharmacological Action: Endogenous erythropoietin (EPO) is a glycoprotein produced in the kidney in response to hypoxia and stimulates the production of red blood cells in the bone marrow from erythroid progenitors, being the key regulator of red blood cells production.
After EPO binds to the receptor on the cell surface, it actives signals interfering with apoptosis and stimulates the proliferation of erythroid cells. Recombinant human erythropoietin (r-hu EPO) produced by recombinant DNA technology is identical in amino acid sequence and has the same biological effects of endogenous urinary erythropoietin.

- Pharmacokinetics: After intravenous administration of erythropoietin alpha, the elimination half-life ranges from 4 to 6 h in healthy volunteers and from 6.5 to 9.3 h in patients with chronic renal failure. After subcutaneous administration, serum levels are lower than those for i.v. route, the levels increase slowly and reach a peak between 12 to 18 h post-dose which is much lower than that achieved for i.v. route (approx. 1/20 of the i.v. value). After subcutaneous administration, erythropoietin levels remain increased for about 72 h. When 3 weekly doses are used, no accumulation is observed, and levels remain stable, whether determined 24 hours after the first injection and 24 hours after the last injection. The subcutaneous bioavailability is 20-30% of the intravenous bioavailability.

- Pharmacodynamics: After administration of erythropoietin alpha, increased reticulocytes within 10 days of starting treatment, followed by increased levels of red blood cells, hemoglobin and hematocrit within 2-6 weeks are observed. The rate of increase of hemoglobin is variable between patients and dose-dependent, but in patients on hemodialysis no higher response at doses greater than 300 IU/kg three times a week was observed.

Dose and administration:

The dosage will be established as medically indicated. Doses should be individualized to ensure the adequate hemoglobin level for each patient.
Recombinant human erythropoietin should be administered under the supervision of a qualified physician.
During treatment, hematological parameters should be monitored regularly. In patients on hemodialysis, the intravenous route is recommended.

Chronic renal failure: In patients with CRF on hemodialysis with venous access available, intravenous route of administration is preferred. It is suggested to administer erythropoietin after the dialysis procedure is completed. In adult patients with CRF without venous access (those who are not yet on hemodialysis or patients on peritoneal dialysis), subcutaneous injection is preferred.
The recommended starting dose of Pronivel in adult patients is 50 to 100 Units/kg three times a week. In children, the available information suggests erythropoietin alpha doses between 25 and 50 UI/kg three times a week.

The treatment is divided into two stages:
- Phase of Correction: 50 IU/kg three times a week.
When a dose adjustment is required, it should be done at least in steps of four weeks. At each step, the increase or reduction in the dose should be of 25 IU/kg three times a week. The total maximum weekly dose should not exceed 3x200 IU/kg.
- Phase of Maintenance: Dose adjustment in order to maintain hemoglobin values at the desired level: Hb between 10 and 12 mg/dL (6.2 to 7.5 mmol/L). The recommended total weekly dose is between 75 and 300 IU/kg.
Patients switching from SC to IV administration should use the same dose, and Hb should be closely monitored (e.g., weekly) to make the necessary adjustments in medication to achieve hemoglobin levels in a proper range.
- Dose adjustments: If the hemoglobin increases and reaches 12 mg/dL, the dose should be reduced by 25%. If it continues to increase, discontinue the dose until the Hb begins to decrease, at which point the dose should be started at a value 25% lower than the last administered dose. If the Hb increases more than 1 mg/dL in 2 weeks, the dose should be decreased by 25%, either in the number of weekly injections, the total amount of EPO alpha in each dose, or both.

Adult patients with cancer: Erythropoietin should only be administered to cancer patients with anemia with Hb below 10 mg/dL. Subcutaneous route of administration is suggested.
The hemoglobin variability should be addressed through dose adjustment, considering the target hemoglobin range between 10 mg/dL (6.2 mmol/L) and 12 mg/dL (7.5 mmol/L), preventing a sustained hemoglobin level above 12 mg/dL.
An initial SC dose of 150 IU/kg three times a week is suggested. If after 4 weeks of treatment, the hemoglobin has increased at least 1 mg/dL (0.62 mmol/L) or the reticulocytes count has increased ≥ 40,000 cells/µL above baseline, the dose should remain at 150 IU/kg three times a week or 450 IU/kg once a week. If the increase in hemoglobin is <1 mg/dL (<0.62 mmol/L) and the reticulocytes count has increased <40,000 cells/µL above baseline, increase the dose to 300 IU/kg 3 times a week. If after an additional 4 weeks of treatment with a dose of 300 IU/kg three times a week, the hemoglobin has increased ≥ 1 mg/dL (≥ 0.62 mmol/L) or the reticulocytes count has increased ≥ 40,000 cells/µL, the dose should remain at 300 IU/kg three times a week. However, if the hemoglobin has increased <1 mg/dL (<0.62 mmol/L) and the reticulocytes count has increased <40,000 cells/µL above baseline, the response is unlikely and the treatment should be discontinued.
Patients should be carefully monitored to ensure that the lowest approved dose of erythropoiesis stimulating agents is used to ensure an adequate control of symptoms of anemia.
Dose adjustments: The risk of thrombotic adverse events could be increased in patients with rapid increases of normal hemoglobin concentrations. (See Precautions).
If the hemoglobin increases 1 mg/dL biweekly or above 2 mg/dL (1.25 mmol/L) a month, or if the hemoglobin is approaching 12 mg/dL (7.5 mmol/L), reduce the dose to 25-50%. If the hemoglobin exceeds 12 mg/dL, discontinue the treatment until the hemoglobin value drops and then restart the treatment with Pronivel with a dose 25% lower than the previous dose.

Adult surgery patients in an autologous pre-donation program: Route of administration: Intravenous. Doses of 300-600 IU/kg twice a week are suggested, for 3 weeks, with at least 200 mg of elemental iron.

Adult patients scheduled for elective surgery
Route of administration: Subcutaneous
Before considering a treatment with erythropoiesis stimulating agents as Pronivel, it is desi-rable to investigate other potential correctable causes of anemia.
The recommended PRONIVEL dosing regimen is 600 IU/kg weekly for three weeks (days -21, -14 and -7) prior to surgery and the day of surgery. If the planned time before surgery is shortened to less than three weeks due to medical needs, EPO alpha 300 IU/kg daily for 10 consecutive days prior to surgery, on the day of surgery and for four days immediately following the surgery should be administered. If when performing hematologic assessments during the preoperative period, the hemoglobin level reaches 15 mg/dL or higher, the administration of Pronivel should be discontinued and subsequent doses should not be are administered.
Adequate iron supplementation: It is recommended to evaluate the levels of iron stores, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin before and during treatment with recombinant human erythropoietin. Most patients will require iron supplements (e.g., elemental iron 200mg orally) to increase or maintain transferrin saturation to levels adequate to support erythropoiesis stimulated by recombinant human erythropoietin. If possible, administer the supplement before initiating the therapy with EPO alpha to achieve the indicated reserves.

Instructions for use:
- All parenteral products should be visually inspected in order to identify any particulate matter and the product keeps colourless
- Do not use any parenteral product if particulate matter or discoloration is observed.
- Avoid prolonged vigorous shaking with subsequent formation of foam, since this procedure can denaturate the protein recombinant human erythropoietin, with the possible inactivation of the product.
- By using aseptic techniques, place a sterile needle in a sterile syringe. Remove the plastic cover (flipp-off) of the vial containing Pronivel solution and clean the top of the stopper with a disinfectant. Insert the needle into the vial and remove with the syringe the appropriate volume of solution to be injected.
- Each vial of Pronivel solution is for a single use because it contains no preservatives. Dispose the unused remaining contents of the vial. Do not reuse the syringe.
- Pronivel solution should not be diluted or administered mixed with other drug solutions.

Administer by subcutaneous or intravenous injection (as appropriate) in 1-2 minutes
Intravenous administration: In 1-2 minutes, at least. In patients on dialysis, injections should be performed after the dialysis, in the catheterization needle, followed by rinsing with 10 mL of isotonic solution for parenteral use to ensure the correct passage of product into the circulation. In patients who develop flu-like symptoms, it may be preferable a slower injection for 5 minutes.
Subcutaneous administration: The maximum volume to be injected per site should not exceed 1 mL. If it is necessary to inject larger volumes, choose more than one site. Injections are made alternately in the limbs and the anterior abdominal wall.

Contraindications:
- Uncontrolled hypertension
- Known hypersensitivity to products derived from mammalian cells.
- Known hypersensitivity to human albumin.
- Known hypersensitivity to any of the excipients of the formulation.
- Patients scheduled for major elective surgery, not participating in autologous blood pre-donation program and not having coronary artery disease, peripheral artery disease, caro-tid arterial disease or stroke, including patients with recent myocardial infarction or stroke.
- Surgical patients who for any reason can not receive adequate antithrombotic prophylaxis.
- Patients developing pure red cell aplasia with any erythropoietin.

Warnings:

Cardiovascular and thrombotic events/increased mortality: An increase in thrombotic vascular events in patients receiving erythropoiesis stimulating agents such as Epo alpha has been observed. These include venous and arterial thrombosis and embolism (including some with fatal outcome), such as deep vein thrombosis, pulmonary embolism, retinal thrombosis and myocardial infarction. Additionally, strokes (including cerebral infarction, cerebral hemorrhage and transient ischemic attacks) has been reported.
An adequate weighting of benefit from treatment with erythropoietin on reported risks of thrombotic events, particularly in patients with previous risk factors, is suggested.
The hemoglobin concentration should also be monitored closely due to the potential risk of thromboembolic events when patients are treated and have Hb concentrations above the range of use.

Use in patients with cancer diagnosis: Erythropoietin is a growth factor that primarily stimulates red cell production. As with all growth factors, there is a concern about the possibility that they stimulate tumor growth. Controlled clinical studies have demonstrated the following:
The use of erythropoiesis stimulating agents shortened the overall survival and increased deaths attributed to disease progression at 4 months in patients with advanced breast cancer, when administered to achieve a hemoglobin level between 12 mg/dL and 14 mg/dL.
Additionally, reduced locoregional control in patients with advanced tumors of head and neck treated with radiation therapy, when given hematopoiesis stimulants agents with a target of hemoglobin higher than 14 mg/dL was reported.
Another erythropoiesis stimulating molecule was shown to increase the risk of death when administered to achieve a hemoglobin level of 12 mg/dL in patients with active malignancy, receiving neither chemotherapy nor radiation therapy.
Considering the above, the decision to administer the recombinant erythropoietin treatment should be based on the benefit-risk assessment with the participation of the patient, taking into account the specific clinical setting. Among the factors to be considered for the evaluation are the type of tumor and its stage, extent of anemia, life expectancy, the setting of treatment and the patient's opinion.
PRONIVEL should only be administered to treat patients with cancer when anemia has appeared after concomitant chemotherapy. A level of hemoglobin of 12 mg/dL should not be exceeded.

Use in patients with chronic renal failure: In patients with chronic renal failure (CRF) a complete blood count (with hemoglobin concentration) should be performed regularly, until a stable level is achieved and periodically thereafter.
In patients with CRF the rate of increase in hemoglobin should be approximately 1 mg/dL and should not exceed 2 mg/dL to minimize the risk of hypertension. The dose should be reduced where hemoglobin approaches to 12 mg/dL.
In two clinical studies, patients with CRF experienced greater risk of death and serious cardiovascular events when erythropoiesis stimulating agents were administered and higher hemoglobin levels were reached.
Patients with CRF with insufficient response to colony-stimulating agents (deficient hemoglobin concentrations) may be at greater risk of cardiovascular events, including death, than other patients.
Shunt thrombosis in patients on hemodialysis has been reported, especially in patients prone to hypotension or whose arteriovenous fistula has complications (e.g., stenosis, aneurysms, etc.). In these patients an early shunt inspection and thrombosis prophylaxis administering a drug such as acetylsalicylic acid is recommended.
In isolated cases, hyperkalemia has been observed, although the causality has not been established. In patients with chronic renal failure monitoring of serum electrolytes is required. If high or increased serum potassium level is observed, then in addition to appropriate treatment of hyperkalemia, the discontinuation of erythropoietin alpha until the serum potassium level has been corrected should be considered.
During therapy with erythropoietin an increase in the dose of heparin during hemodialysis due to the

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increased volume of the cell mass is often required. If heparinization is not optimal a potential blockage in the dialysis system may occurs. Adjustment may be required to prevent the clogging of the extracorporeal circuit during hemodialysis.
In some women with CRF, menses have restarted after therapy with EPO alpha, so the possibility of pregnancy should be discussed and the need for contraception should be evaluated.
Based on the information available to date, correction of anemia with EPO alpha in adult patients with chronic renal failure not yet undergoing dialysis does not accelerate the rate of progression of renal failure.
Surgical patients included in an autologous pre-donation program: All warnings and special precautions associated with autologous pre-donation programs, especially those related to routine volume replacement, should be followed.
Patients scheduled for elective surgery: There is increased risk of postoperative thrombotic events in patients with hemoglobin greater than 13 mg/dL.
In patients scheduled for elective surgery the cause of anemia should be determined and treated, if possible, before initiating treatment with recombinant erythropoietin. Thrombotic events can be a risk in this population, so they should be weighed carefully.
Hypertension: Blood pressure should be controlled before initiation of therapy with recombinant human erythropoietin and during treatment.
Patients with uncontrolled hypertension should not be treated with recombinant human erythropoietin (see Contraindications).
Blood pressure may increase during treatment of anemia with EPO. Seizures and encephalopathy has been observed.
Patients should be advised of the importance of compliance with antihypertensive therapy and dietary restrictions. If the blood pressure is difficult to control with the initial appropriate measures, may be necessary to reduce the dose of recombinant human erythropoietin or discontinue the therapy until the hemoglobin concentration begins to descend.
Seizures: Seizures in patients receiving recombinant human erythropoietin have occurred. Use cautiously in patients with epilepsy, a history of seizures, conditions associated with predisposition to seizure activity as central nervous system infections or brain metastases.
Pure red blood cells aplasia: Cases of red blood cells aplasia and severe anemia, with or without cytopenias, mostly associated with neutralizing antibodies to erythropoietin has been reported.
It has been reported predominantly in patients with pure red cell aplasia receiving erythropoietin subcutaneously. It was rarely reported after months or years of treatment with erythropoietin, there were also rare cases in patients with hepatitis C treated with ribavirin and interferon concomitantly to erythrocytes stimulating agents. The use of hematopoiesis-stimulating agents in patients with anemia associated with hepatitis C is not approved.
Any patient having decreased therapeutic response to erythropoietin should be evaluated for the etiology of loss of therapeutic effect, including typical causes of non-response. If no cause is identified, examination of bone marrow should be considered.
If pure red blood cells aplasia is diagnosed, PRONIVEL should be discontinued immediately and antibody detection should be considered. If erythropoietin and other erythropoietic products antibodies are detected, erythropoietin should be discontinued permanently, and switching to another erythropoiesis stimulant agent should not be performed, as there may be cross-reactive antibodies.

Precautions:
Iron supplements: Before starting treatment with PRONIVEL, other causes of anemia (iron deficiency, hemolysis, blood loss, deficiency of vitamin B12 or folate) should take into account and treated. In most cases, serum ferritin drops simultaneously with the increase in hematocrit. In order to ensure optimum response to Pronivel, suitable iron deposits should be ensured, so supplements should be administered if necessary, usually 200-300mg/day daily:
In patients with chronic renal failure whose serum ferritin levels are below 100 ng/mL a supplement of oral iron of e.g. 200-300 mg/day is recommended (100-200 mg/day for pediatric patients).
In patients with cancer whose transferrin saturation is below 20% a supplement of oral iron of 200-300 mg/day is recommended.
In patients on a pre-donation program, oral elemental iron 200 mg/day should be administered several weeks before.
In patients undergoing elective surgery, oral iron 200 mg/day should be administered prior to Pronivel, if possible, and if not during treatment.
If the patient does not respond or maintain the response, the following etiologies should be evaluated and considered:
1- Iron deficiency.
2- Underlying malignant, infectious or inflammatory processes.
3- Occult blood loss.
4- Underlying hematological diseases (thalassemia, refractory anemia or other myelodysplastic disorders).
5- Vitamin deficiencies (vitamin B12, folic acid).
6- Hemodialysis.
7- Aluminum poisoning.
8- Fibrous cystic osteitis.

- Pronivel contains **albumin** derived from human blood. Based on the effective donor screening and product manufacturing process, this would lead to a rare remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt Jacob disease (CJD) is considered remote. No cases of transmission of viral diseases or CJD identified associated with albumin has been reported.
- Serious allergic reactions: With the use of an erythropoietin alpha such as Pronivel, a serious allergic reaction, including anaphylactic reaction, angioedema, bronchospasm, rash, and urticaria may develop. If a serious allergic or anaphylactic reaction occurs, discontinue immediately the Pronivel therapy and consult your doctor.
- The various erythropoiesis stimulating factors are not necessarily equivalent, so it is important to consult your health care professional before making any changes.
- Platelet counts during the first 8 weeks of treatment with Pronivel are suggested as a dose-dependent increasing in platelets may occurs which becomes normal during therapy. Thrombocytopenia has been also reported.
- Use with caution in patients with gout, as increased uric acid could be observed.
- Use with caution in patients with chronic liver disease, as these patients may have increased erythropoiesis.

Pregnancy: Category B3 (Australia): It is not known if Pronivel crosses the placenta or if it can produce fetal harm when administered to a pregnant woman. There are no adequate and well controlled studies in pregnant women. Studies in rats showed that doses of 20-500 IU/kg/day produced decreased fertility, increased losses, decreased fetal weight, and delayed ossification. Recombinant human erythropoietin can be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Breastfeeding: It is not known if recombinant human erythropoietin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when administered recombinant human erythropoietin to breastfeeding mothers. Exposed animals showed retarded growth and development of offspring.
Pediatric use: There are clinical trials supporting the effect of erythropoietin alpha in children as to correction of anemia, reduced transfusion requirements, improved bleeding tendency in uremia, increased appetite, decreased cytotoxic antibodies.
Safety reported for pediatric patients is incomplete, particularly with regard to hemoglobin range management and changes in blood pressure.
Genotoxicity: EPO alpha did not induce gene mutations nor caused chromosomal damage.
Carcinogenicity: There are conflicting reports in literature regarding the potential role in tumor proliferation of erythropoietin stimulating agents, however, long-term studies have not been conducted.

Drugs Interactions:
The effect of recombinant human erythropoietin can be enhanced by simultaneous administration of another anti-anemia agent. Therefore, administration of iron when treatment with recombinant human erythropoietin does not produce the desired response should be done carefully considering laboratory controls made.
Drugs lowering erythropoiesis may decrease the response to Pronivel.
Cyclosporine may interact. It is suggested to monitor their blood levels and adjust for any increase in hematocrit.
The administration of trastuzumab 6 mg/kg in patients with metastatic breast cancer along to EPO alpha 40,000 IU/mL did not affect the pharmacokinetics of trastuzumab.
Effects on the ability to operate machines: No studies have been conducted regarding erythropoietin and the ability of driving vehicles and operate machines.

Adverse Reactions:
Studies indicate that recombinant human erythropoietin is generally well tolerated.
The most frequently reported adverse event to the treatment with erythropoietin alpha is increased blood pressure or worsening of preexisting hypertension. Monitoring of blood pressure, especially at the beginning of treatment is recommended. Hypertensive crisis with encephalopathy, which requires immediate medical attention and intensive care in patients with low or normal blood pressure has been reported during treatment with erythropoietin. It is advised to pay special attention to sudden stabbing migraine-like headaches as a possible warning signal.
In patients receiving erythropoiesis-stimulating agents an increased incidence of thrombotic vascular events has been observed.
Hypersensitivity reactions such as rash (including urticaria), anaphylactoid reactions and angioedema have also been reported.
Other most frequently reported events (≥10%) in clinical trials are diarrhea, nausea, vomiting, pyrexia, chills, injection site reactions, headache, and flu-like syndrome (especially at the start of treatment).
Adverse events occurred in more than 5% of patients with chronic renal failure participating in several clinical trials were hypertension, thromboembolism (mainly in patients on dialysis), rash, diarrhea, nausea, vomiting, arthralgia, limbs pain, muscle aches, bone pain, chills, peripheral edema, injection site reactions, flu-like syndrome, pyrexia, hyperkalemia, dizziness, upper respiratory tract infections, cough.
In more than 5% of patients with anemia due to cancer chemotherapy treated with erythropoietin in various clinical trials, nausea, vomiting, diarrhea, pyrexia, peripheric edema, headache, cough, embolism and thrombosis, myalgia, arthralgia, stomatitis, cough, weight loss, leukopenia, bone pain, rash, hyperglycemia, insomnia, headache, depression, dysphagia, hypokalemia, and thrombosis and embolism have been described.
Adverse reactions occurred in ≥5% of surgical patients in clinical trials were: nausea, vomiting, diarrhea, chills, itching, injection site reactions, pyrexia, peripheral edema, headache, cough, embolism and thrombosis, deep venous thrombosis, hypertension.
Allergic reactions: There were no reports of serious allergic reactions or anaphylaxis associated with the administration of recombinant human erythropoietin. In patients with chronic renal failure rash and urticaria of moderate and transient nature were rarely observed.
However, if an anaphylactic reaction occurs, therapy with recombinant human erythropoietin should be immediately discontinued and appropriate therapy should be initiated. In HIV-infected patients treated with zidovudine developing urticarial reactions, this event was related to immunosuppression induced by HIV or prior exposure to blood products.
Immunogenicity: As with all therapeutic proteins, there is a potential for immunogenicity. In patients receiving recombinant human erythropoietin, erythropoietin neutralizing antibodies, in association with recombinant human erythropoietin or severe anemia with or without other cytopenias have been reported.
When reported, the incidence of antibody formation is high depending on the sensitivity and specificity of the assay.
Additionally, the observed incidence of positive antibodies (including neutralizing antibodies) in an assay may be influenced by several factors including assay methodology, sampling, sample collection time, concomitant medications, and underlying disease.
For these reasons the comparison of the incidence of cross-antibodies within this class (erythropoietic proteins) may be an unclear data.
Hypertension: Up to 80% of patients with chronic renal failure have a history of hypertension. The blood pressure may rise during therapy with recombinant human erythropoietin in patients with chronic renal failure (on dialysis or not). During the early phase of treatment when the hematocrit is increasing, approximately 25% of patients on dialysis may require antihypertensive therapy.
Seizures: In patients with chronic renal failure, the relationship between therapy with recombinant human erythropoietin and seizures is uncertain. However, it seems to have a higher rate of seizures during the first 90 days of therapy (occurring in approximately 2.5% of patients), when compared with subsequent periods.
In clinical trials with recombinant human erythropoietin in HIV-infected patients treated with zidovudine, 10 patients experienced seizures. In general, these events seem to be related to an underlying disease such as meningitis or brain neoplasm and not to therapy with recombinant human erythropoietin.
Thrombotic events: During hemodialysis, patients treated with recombinant human erythropoietin may require an increase in heparin anticoagulation. A statistical link between increased hematocrit and rate of thrombotic events has not been established. In patients with chronic renal failure (on dialysis or not) thrombotic events such as myocardial infarction, stroke, and transient ischemic attack have occurred.
Patients with chronic renal failure: In all clinical studies the administration of recombinant human erythropoietin was generally well tolerated, regardless of the route of administration.
Reported events occurred within several hours after administration of recombinant human erythropoietin were rare, mild and transient and included flu-like symptoms such as arthralgia and myalgia.
In clinical studies with recombinant human erythropoietin in patients on dialysis, the most frequently reported adverse effects were: hypertension; headache; tachycardia; nausea/vomiting; clot in vascular access; shortness of breath; hyperkalemia and diarrhea.
Other reported side effects were: arthralgia; edema; fatigue; chest pain; skin reaction (at the site of administration); asthenia; vertigo; convulsion; stroke; transient ischemic attack, and myocardial infarction.
Patients with cancer on chemotherapy: In double-blind, placebo-controlled studies, although some statistically significant differences between patients treated with recombinant human erythropoietin and those treated with placebo were noted, the overall safety profile of recombinant human erythropoietin appears to be consistent with the process of the advanced cancer disease. The observed adverse effects were pyrexia; diarrhea; nausea; vomiting; edema; asthenia; fatigue; shortness of breath; paresthesia; upper respiratory infection; dizziness and chest pain.
The available data from tumor models in animals and measurements of proliferation of solid tumor cells from clinical biopsy specimens in response to recombinant human erythropoietin, suggest no enhancement of tumor growth. However, as a growth factor, the possibility that human recombinant erythropoietin may enhance the growth of some tumors, particularly myeloid tumors, can not be excluded.
HIV-infected patients treated with zidovudine: In double-blind, placebo-controlled studies there was no significant difference between treatment groups in the incidence of the events listed below: pyrexia, fatigue, headache, cough, diarrhea, rash, respiratory congestion, nausea, shortness of breath, asthenia, skin reaction (at the site of administration), vertigo.
Recombinant human erythropoietin was not associated with significant increases in opportunistic infections or mortality. The serum antigen levels seem not to increase. Preliminary data showed no increase in HIV replication in "in vitro" infected cell lines.
In post-marketing experience, pure red blood cells aplasia, which has been linked to anti-erythropoietin antibodies, was reported very rarely (<1/10,000).

Overdose
The maximum amount of recombinant human erythropoietin that can be safely administered in single or multiple doses has not been determined. The response to erythropoietin administration is individual and dose-related.
Therapy with recombinant human erythropoietin may result in polycythemia if the hematocrit is not carefully controlled and the dose is not adjusted. If the target range is exceeded, recombinant human erythropoietin may be discontinued temporarily until the hematocrit return to the target range; then the therapy with recombinant human erythropoietin may be resumed using a lower dose (see Dosage and Administration). Precautions: Hypertension and seizures. If polycythemia is a concern, phlebotomy in order to reduce the hematocrit may be started.
In the event of overdose, go to the nearest hospital or contact a Poison Control Center:

How Supplied
Packages containing: 1 prefilled syringe with 1 mL of solution with needle.
Packages containing: 1 vial of 1 mL.
Hospital use: Packages containing 10, 25, 50 and 100 vials of 1 mL.

Conservation and storage conditions
Store at a temperature between 2 ºC - 8 ºC, protected from light. Do not freeze or shake.

MAINTAIN THIS AND ALL THE MEDICINES IN THEIR ORIGINAL PACKAGE AND OUT OF THE CHILDREN REACH.

Medicinal product authorized by the Ministry of Health. Certificate No. 43.661
LABORATORIO ELEA PHOENIX S.A.: Av. Gral. Lemos N° 2809, Malvinas Argentinas, Buenos Aires, Argentine.
Technical Director: Laura A. B. Hernández, Pharmacist.
Date of authorization: August 1994
Date of revision: August 2019
Manufactured by: M.R. PHARMA S.A.: Estados Unidos N° 5105, El Triangulo, Malvinas Argentinas, Provincia de Buenos Aires, República Argentina. **For: LABORATORIO ELEA PHOENIX S.A.:** Av. Gral. Lemos N° 2809, Malvinas Argentinas, Buenos Aires, Argentine.
Epoetin Alfa 2.000 I.U./ml, solution for injection (IV/SC)
Imported and Distributed by: Biocare Lifesciences, Inc., 4th Floor, 393 Goodwill Bldg., Senator Gil Puyat Ave., Brgy. Bel-Air, Makati, Metro Manila.
Epoetin Alfa 4.000 I.U./ml, solution for injection (IV/SC)
Imported and Distributed by: Biocare Lifesciences, Inc., 4th Floor, 393 Goodwill Bldg., Senator Gil Puyat Ave., Brgy. Bel-Air, Makati, Metro Manila.

biocare LIFESCIENCES INC ELEA

	Diseñador Gráfico	Desarrollo Packaging	Garantía de la calidad (Fla./Cons.)	Control Comercial (Nacionales)	Control Comercial (Exportaciones)	Control Médico (Dir. Médica)	Desarrollo Galénico (Fórmula)	Control de Marcas (Marcas/Patentes)	Control Regulatorio (Exportaciones)	Control Regulatorio (Nacionales)	Aprobación Final (Dir. Técnica)	Control archivo Final
Fecha												
Firma												
Aclaración (Completa)	Paula Magdalena											Paula Magdalena
Observaciones												

CADA CONTROL DEBERÁ REALIZARSE EN UN PLAZO NO MAYOR A 2 DÍAS HÁBILES