Epoetin Alfa Rx

Pronivel®

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 1.587 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 1.587 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:*
• 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 anemia of renal origin accompanied by clinical symptoms in patients.
- *Indicated for the treatment of anemia and reduction of transfusion requirements in patients undergoing chemotherapy for solid tumors, malignant lymphoma or multiple myeloma, and at risk for 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 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 (4 units or more units of blood for females or 5 or more units for males).
- *Indicated for non-iron deficient adults prior to major elective orthopaedic surgery having a risk for transfusion complications to reduce exposure to allogeneic blood transfusion.* Use is restricted to patients with moderate anemia (e.g. hemoglobin concentration range 10 to 13 g/dl) who do not have an autologous predonation programme available and with expected 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 by stimulating 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 the proliferation and stimulates the proliferation of erythroid cells. Recombinant human erythropoietin (rHuEPO) 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 clinical 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, reaching 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 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 third injection. The subcutaneous bioavailability is 20-30% of the intravenous bioavailability.
- *Pharmacodynamics:* After administration of erythropoietin alpha, increased reticulocyte counts appear in 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 is 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 achieve an 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: Patients with CRF on hemodialysis with venous access available, the intravenous route of administration is preferred. It is suggested to administer erythropoietin at the end of the procedure is completed. In adult patients with CRF without venous access (those who are not undergoing hemodialysis or patients on peritoneal dialysis), subcutaneous injection is preferred.
The recommended starting dose of Pronivel in adult patients is 50 to 100 Unit/kg three times a week. In children, the available information suggests erythropoietin alpha doses between 50 and 100 IU/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. The dose should be increased in steps of 25 IU/kg three times a week. The maximum dose of 300 IU/kg three times a weekly dose should not exceed 3x200 IU/kg.
- Phase of Maintenance: Dose adjustment in order to maintain hemoglobin values stable in the range 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 levels should be monitored (e.g., weekly) to make the necessary adjustments in medication to achieve the desired 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; then restart the treatment at a dose 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 administrations or in 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 hemoglobin range between 10 mg/dL (6.2 mmol/L) and 12 mg/dL (7.5 mmol/L) is recommended to 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 increased in absolute 40,000 cells/µL above baseline, the dose should remain at 150 IU/kg three times 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. After 4 weeks of treatment with a dose of 300 IU/kg three times a week, if 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 increases to above 12 mg/dL (<0.62 mmol/L) and the reticulocytes count has increased <40,000 cells/µL, the dose should be reduced by 25% or the treatment should be discontinued.
Patients should be carefully monitored to ensure that the lowest approved dose of an erythropoiesis stimulating agents is used to ensure an adequate control of symptoms of anemia. In patients with chronic renal failure monitoring of serum electrolytes is required. If high or increased Dose adjustments: The risk of thrombotic adverse events could be increased in patients with elevated increases of normal hemoglobin concentrations. (See Precautions).
If the hemoglobin increases 1 mg/dL biweekly or above 2 mg/dL (1.25 mmol/L) in any two consecutive weeks, 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.
In surgery patients in an autologous pre-donation program: Route of administration: Intravenous.
Administer 300 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
Prior to initiating a treatment with erythropoiesis stimulating agents as Pronivel, it is desirable 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 administered.
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 for erythropoiesis stimulated by recombinant human erythropoietin. If possible, administer the iron supplement before initiating the therapy with EPO alpha to achieve the indicated reserves.

Instructions for use:
Pronivel products should be visually inspected in order to identify any particulate matter and/or any alteration in colour.
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.
Using aseptic techniques, place a sterile needle in a sterile syringe. Remove the plastic cover from the top 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 Pronivel solution. 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.
• Injection should be administered in 1-2 minutes, at least. In patients on dialysis, injections should be administered at the end of the dialysis, in the catheterization needle, followed by rinsing with 10 mL of isotonic solution of parenteral use to ensure the correct passage of product into the circulation. In patients who develop flushing symptoms, it may be preferable a slower injection for 5 minutes.
• Intramuscular administration: Maximum volume to be injected per site should not exceed 1 mL. If more than 1 mL is to be injected, inject larger volumes, choose more than one site. Injections are made alternately in the upper lateral quadrants of 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 programme.
• Patients with coronary artery disease, peripheral artery disease, cerebrovascular disease (CVD), 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
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 venous thrombosis, pulmonary embolism, retinal thrombosis and myocardial infarction. Additionally, strokes (including cerebral infarction, cerebral hemorrhage and transient ischemic attack) have been reported.
The risk/benefit of benefit from treatment with erythropoietin on reported risks of thrombotic events 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.
Due to an old hypothesis that 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 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 radiotherapy, when given hematopoiesis stimulants agents with a target of hemoglobin higher than 14 mg/dL have been 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 a risk/benefit assessment with the participation of the patient, taking into account the specific clinical situation. The factors to be considered for the evaluation are the type of tumor and the stage, extent of disease, anemia, life expectancy, the setting of treatment and the patient's opinion
Body detection should be considered. If erythropoietin and other erythropoietic products are administered to treat patients with cancer when anemia persists or reappears after detected, erythropoietin should be discontinued permanently, and switching to another erythropoietin stimulant agent should not be performed, as there may be cross-reactive antibodies.

Precautions:
Iron supplementation: Before starting treatment with PRONIVEL, other causes of anemia such as hemolysis, blood loss, deficiency of vitamin B12 or folate) should take into account and treated. In cases, serum ferritin drops simultaneously with the increase in hematocrit. In order to achieve a 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, administration 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 pro-donation program, oral elemental iron 200 mg/day should be administered for several weeks before.
In patients undergoing elective surgery, oral iron 200 mg/day should be administered for several weeks if possible, and if not during treatment.
If the patient does not respond or maintain the response, the following etiologies should be investigated 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 hemolytic 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 the 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. There is no evidence 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, serious anaphylactic reaction, including anaphylactic reaction, angioedema, bronchospasm, rash, and urticaria may develop. If a serious allergic or anaphylactic reaction occurs, discontinue immediately the therapy and consult your doctor.
- The various erythropoiesis stimulating factors are not necessarily equivalent, so it is necessary consult your health care professional before making any changes.
- Platelet counts during the first 8 weeks of treatment with Pronivel are suggested as a precaution. An increasing in platelets may occurs which becomes normal during therapy. Thrombocythemia 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 are not suitable for erythropoiesis.

Pregnancy: Category B3 (Australian): 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 embryotoxicity, 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 administering recombinant human erythropoietin to breastfeeding mothers. Exposed animals showed no adverse effects on development of offspring.
Pediatric use: There are clinical trials supporting the effect of erythropoietin alpha-in children with reduction of anemia, reduced transfusion requirements, improved bleeding tendency in neonatal, improved appetite, decreased cytotoxic antibodies.
Safety reported for pediatric patients is incomplete, particularly with regard to long-term 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 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 erythropoietin does not produce the desired response should be done carefully and with controls made.
Drugs lowering erythropoiesis may decrease the response to Pronivel.
Cyclosporine may interact. It is suggested to monitor their blood levels and adjust the dose in hematocrit.
The administration of trastuzumab 6 mg/kg in patients with metastatic breast cancer and 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 the ability 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 a worsening of 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 age in the dialysis system may occurs. Adjustment may be required to prevent thrombosis of the extracorporeal circuit during hemodialysis.
In some women with CRF, menses have restarted after therapy with EPO alpha, ovulation has also been reported.
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 is not associated with a worsening of renal function in patients with chronic renal failure not yet undergoing dialysis does not accelerate the rate of decline of renal function.
Surgical patients included in an autologous pre-donation programme and special procedures associated with autologous pre-donation programs, especially those related to cardiac or vascular replacement, should be followed.
Patients scheduled for elective surgery: 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 occur 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 have 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, it may be advisable to reduce the dose of recombinant human erythropoietin or discontinue the treatment if hemoglobin concentration begins to descend.
Seizures: Seizures in patients receiving recombinant human erythropoietin have occurred. Uncontrolled or poorly controlled in patients with epilepsy, a history of seizures, conditions associated with increased risk of 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 other cytopenias, mostly associated with neutralizing antibodies to erythropoietin has been reported.
It has been reported predominantly in patients with pure red cell aplasia related to the administration of subsequently, it was rarely reported after months or years of treatment without immunosuppressive therapy. These cases were also rare cases in patients with hepatitis C treated with ribavirin and interferon, in patients with myelodysplastic 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 blood cells are found, bone marrow examination of bone marrow should be considered.
If pure red blood cells aplasia is diagnosed, PRONIVEL should be discontinued immediately and if antibodies are detected, the treatment should be permanently discontinued, and switching to another erythropoietin stimulant agent should not be performed, as there may be cross-reactive antibodies.

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Carcinogenicity: There are conflicting reports in literature regarding the potential role 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 erythropoietin does not produce the desired response should be done carefully and with controls made.
Drugs lowering erythropoiesis may decrease the response to Pronivel.
Cyclosporine may interact. It is suggested to monitor their blood levels and adjust the dose in hematocrit.
The administration of trastuzumab 6 mg/kg in patients with metastatic breast cancer and 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 the ability 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 a worsening of 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 age in the dialysis system may occurs. Adjustment may be required to prevent thrombosis of the extracorporeal circuit during hemodialysis.
In some women with CRF, menses have restarted after therapy with EPO alpha, ovulation has also been reported.
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 is not associated with a worsening of renal function in patients with chronic renal failure not yet undergoing dialysis does not accelerate the rate of decline of renal function.
Surgical patients included in an autologous pre-donation programs and special procedures associated with autologous pre-donation programs, especially those related to cardiac or vascular replacement, should be followed.
Patients scheduled for elective surgery: 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 occur 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 have 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, it may be advisable to reduce the dose of recombinant human erythropoietin or discontinue the treatment if hemoglobin concentration begins to descend.
Seizures: Seizures in patients receiving recombinant human erythropoietin have occurred. Uncontrolled or poorly controlled in patients with epilepsy, a history of seizures, conditions associated with increased risk of 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 other cytopenias, mostly associated with neutralizing antibodies to erythropoietin has been reported.
It has been reported predominantly in patients with pure red cell aplasia related to the administration of subsequently, it was rarely reported after months or years of treatment without immunosuppressive therapy. These cases were also rare cases in patients with hepatitis C treated with ribavirin and interferon, in patients with myelodysplastic 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 blood cells are found, bone marrow examination of bone marrow should be considered.
If pure red blood cells aplasia is diagnosed, PRONIVEL should be discontinued immediately and if antibodies are detected, the treatment should be permanently discontinued, and switching to another erythropoietin stimulant agent should not be performed, as there may be cross-reactive antibodies.

Precautions:
Iron supplementation: Before starting treatment with PRONIVEL, other causes of anemia such as deficiency of vitamin B12 or folate) should take into account and treated. In cases, serum ferritin drops simultaneously with the increase in hematocrit. In order to achieve a 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, administration 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 pro-donation program, oral elemental iron 200 mg/day should be administered for several weeks before.
In patients undergoing elective surgery, oral iron 200 mg/day should be administered for several weeks if possible, and if not during treatment.
If the patient does not respond or maintain the response, the following etiologies should be investigated 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 hemolytic 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 the 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. There is no evidence 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, serious anaphylactic reaction, including anaphylactic reaction, angioedema, bronchospasm, rash, and urticaria may develop. If a serious allergic or anaphylactic reaction occurs, discontinue immediately the therapy and consult your doctor.
- The various erythropoiesis stimulating factors are not necessarily equivalent, so it is necessary consult your health care professional before making any changes.
- Platelet counts during the first 8 weeks of treatment with Pronivel are suggested as a precaution. An increasing in platelets may occurs which becomes normal during therapy. Thrombocythemia 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 are not suitable for erythropoiesis.

Pregnancy: Category B3 (Australian): 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