**PRODUCT NAME**
EPREX® (Epoetinum alfa) Pre-filled Syringes with needle guard (PROTECS™)

**DOSAGE FORMS AND STRENGTHS**
Epoetinum alfa, a glycoprotein produced by recombinant DNA technology, is the active ingredient. Epoetinum alfa is a sterile, clear, colorless, buffered parenteral solution for intravenous or subcutaneous injection.

<table>
<thead>
<tr>
<th>Concentration of Epoetinum alfa g</th>
<th>Volume per syringe (mL)</th>
<th>International Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>8.4</td>
<td>0.5</td>
</tr>
<tr>
<td>2000</td>
<td>16.8</td>
<td>0.5</td>
</tr>
<tr>
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<td>0.3</td>
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</tr>
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<tr>
<td>40000</td>
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</tr>
</tbody>
</table>

For excipients, see List of Excipients.

**CLINICAL INFORMATION**

**Indications**
EPREX® is indicated for the treatment of anemia associated with chronic renal failure in adult patients on hemodialysis and peritoneal dialysis, and in pediatric patients on hemodialysis.

EPREX® is indicated for the treatment of severe anemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing dialysis.

EPREX® is indicated for the treatment of anemia and reduction of transfusion requirements in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

EPREX® is indicated for the treatment of anemia in adult HIV infected patients being treated with zidovudine having endogenous erythropoietin levels ≤500 mU/mL.

EPREX® is indicated in adults to facilitate autologous blood collection within a predeposit program and decrease the risk of receiving allogeneic blood transfusions in patients with moderate anemia (hematocrits of 33-39%, hemoglobin of 10-13 g/dL, [6.2-8.1 mmol/L], no iron deficiency), who are scheduled for major elective surgery and are expected to require more blood than that which can be obtained through autologous blood collection techniques in the absence of EPREX®. Treatment should only be given to patients 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).

EPREX® is indicated to augment erythropoiesis in the perisurgical period in order to reduce allogeneic blood transfusions and correct postoperative anemia in adult non-iron deficient patients undergoing major elective orthopedic surgery. Use should be restricted to patients with moderate anemia (e.g. Hb 10-13 g/dL) who do not have an autologous predonation program available and with expected moderate blood loss (900 to 1800 mL).

**Dosage and Administration**

**Method of Administration**
EPREX® may be administered by intravenous or subcutaneous injection.

As for any parenterally administered drug, the injection solution should be inspected for particles and discoloration prior to administration. Do not shake; shaking may denature the glycoprotein, rendering it inactive.

EPREX® in syringes contains no preservatives. Do not re-use syringe. Discard unused portion.

**Intravenous Injection**
EPREX® should be administered over at least one to five minutes, depending on the total dose.
A slower injection may be preferable in patients who react to the treatment with flu-like symptoms. In hemodialysis patients, a bolus injection may be given during dialysis via a suitable venous port in the dialysis line. Alternatively, at the completion of a hemodialysis session, the injection can be given via the fistula needle tubing, followed by 10 mL of isotonic saline to rinse the tubing and to ensure satisfactory injection of the product into the circulation. EPREX® should not be administered by intravenous infusion or mixed with other drugs.

**Subcutaneous Injection**
The maximum volume per injection site should be 1 mL. In case of larger volumes, more than one injection site should be used. The injections should be given in the limbs or the anterior abdominal wall.

**Chronic Renal Failure Patients**
In patients with chronic renal failure where intravenous access is routinely available (hemodialysis patients), administration by the intravenous route is preferable. Where intravenous access is not readily available (patients not yet undergoing dialysis and peritoneal dialysis patients), EPREX® may be administered subcutaneously.

The hemoglobin concentration aimed for should be between 10 to 12 g/dL (6.2-7.5 mmol/L) in adults and 9.5 to 11 g/dL (5.9-6.8 mmol/L) in children.

In patients with chronic renal failure, maintenance hemoglobin concentration should not exceed the upper limit of the hemoglobin concentration range (see Warnings and Precautions - Renal Failure Patients).

When changing the route of administration, the same dose should be used initially and then titrated to keep hemoglobin in the hemoglobin concentration range.

In the correction phase, the dose of EPREX® should be increased if the hemoglobin does not increase at least 1 g/dL (0.62 mmol/L) per month.

A clinically significant increase in hemoglobin is usually not observed in less than 2 weeks and may require up to 6-10 weeks in some patients.

When the hemoglobin concentration is within range, the dose should be decreased by 25 IU/kg/dose in order to avoid exceeding the hemoglobin concentration range. Dose should be reduced when hemoglobin approaches 12 g/dL.

Dose reductions may be made by omitting one of the weekly doses or by decreasing the amount of each dose.

**Adult Hemodialysis Patients**
In patients on hemodialysis, where intravenous access is readily available, administration by the intravenous route is preferable.

The treatment is divided into two stages:

**Correction phase**
50 IU/kg three times per week.

When necessary, dose adjustments should be made in increments of 25 IU/kg three times per week at intervals of at least 4 weeks until the hemoglobin concentration range (10-12 g/dL [6.2-7.5 mmol/L]) is achieved.

**Maintenance phase**
Appropriate adjustment of the dose should be made in order to maintain the hemoglobin concentration within the desired range between 9.5 g/dL to 11 g/dL (5.9 to 6.8 mmol/L).

**Pediatric Hemodialysis Patients**

**Correction phase**
50 IU/kg three times per week.

When necessary, dose adjustments should be made in increments of 25 IU/kg three times per week at intervals of at least 4 weeks until the hemoglobin concentration range (9.5-11 g/dL [5.9-6.8 mmol/L]) is achieved.

**Maintenance phase**
Appropriate adjustment of the dose should be made in order to maintain the hemoglobin concentration within the desired range between 9.5 g/dL to 11 g/dL (5.9 to 6.8 mmol/L).
Maintenance phase
During the maintenance phase, EPREX® can be administered either 3 times per week, and in the case of subcutaneous administration, once weekly or once every 2 weeks.

Appropriate adjustment of dose and dose intervals should be made in order to maintain hemoglobin values at the desired level: Hb between 10 and 12 g/dL (6.2-7.5 mmol/L). Extending dose intervals may require an increase in dose.

The maximum dosage should not exceed 150 IU/kg 3 times per week, 240 IU/kg (up to a maximum of 20000 IU) once weekly, or 480 IU/kg (up to a maximum of 40000 IU) once every 2 weeks.

Cancer Patients

Adult Cancer Patients
The subcutaneous route of administration should be used.

The hemoglobin concentration range should be 10 to 12 g/dL (7.5 mmol/L) in men and women and it should not be exceeded.

Epoetinum alfa therapy should continue until one month after the end of chemotherapy. However, the need to continue Epoetinum alfa therapy should be re-evaluated periodically.

The initial dose for the treatment of anemia should be 150 IU/kg 3 times per week.

Alternatively, EPREX® can be administered at an initial dose of 40000 IU subcutaneously once weekly.

If after 4 weeks of treatment at the initial dose, the hemoglobin has increased by at least 1 g/dL (0.6 mmol/L) [or the reticulocyte count has increased ≥40000 cells/μL above baseline] the dose should remain unchanged.

If after 4 weeks of additional therapy with 300 IU/kg 3 times per week or 60000 IU weekly, the hemo-
mined prior to transfusion. Available data suggest that patients with endogenous serum erythropoietin levels >500 mU/mL are unlikely to respond to therapy with EPREX®.

The treatment is divided into two stages:

**Correction phase**

100 IU/kg three times per week by the subcutaneous or intravenous route for 8 weeks. If the response is not satisfactory (i.e., reduced transfusion requirements or increased hemoglobin) after 8 weeks of therapy, the dose of EPREX® can be increased. Dose increases should be made in increments of 50 to 100 IU/kg three times per week at intervals of at least 4 weeks. If patients have not responded satisfactorily to a dose of 300 IU/kg three times per week, it is unlikely that they will respond to higher doses.

**Maintenance phase**

After the desired response is attained, the dose should be titrated to maintain the hematocrit between 30-35%, based on factors such as variations in zidovudine dose and the presence of intercurrent infections or inflammatory episodes. If the hematocrit exceeds 40%, the dose should be discontinued until the hematocrit decreases to 36%. When treatment is resumed, the dose should be reduced by 25% and then titrated to maintain the desired hematocrit.

In zidovudine-treated HIV-infected patients the hemoglobin concentration should not exceed 12 g/dL (7.5 mmol/L).

### Adult Surgery Patients in an Autologous Pre-Donation Program

The intravenous route of administration should be used. EPREX® should be administered after the completion of each blood donation procedure.

Mildly anemic patients (hematocrit of 33 to 39% and/or hemoglobin 10 to 13 g/dL [6.2-8.1 mmol/L]) requiring predeposit [of ≥4 units] of blood should be treated with EPREX® at 600 IU/kg 2 times weekly for 3 weeks prior to surgery.

For those patients who require a lesser degree of erythropoietic stimulation, a dose regimen of 150-
Warnings and Precautions

General
In all patients receiving EPREX®, blood pressure should be closely monitored and controlled as necessary. EPREX® should be used with caution in the presence of untreated, inadequately treated or poorly controllable hypertension.

It may be necessary to initiate or increase antihypertensive treatment during Epoetinum alfa therapy. If blood pressure cannot be controlled, Epoetinum alfa treatment should be discontinued.

EPREX® should be used with caution in patients with epilepsy, history of seizures, or medical conditions associated with a predisposition to seizure activity such as CNS infections and brain metastases.

EPREX® should be used with caution in patients with chronic liver failure. The safety of Epoetinum alfa has not been established in patients with hepatic dysfunction. Due to decreased metabolism, patients with hepatic dysfunction may have increased erythropoiesis with Epoetinum alfa.

An increased incidence of thrombotic vascular events (TVEs) has been observed in patients receiving ESAs (see Undesirable Effects). These include venous and arterial thromboses and embolism (including some with fatal outcomes), such as deep venous thrombosis, pulmonary emboli, retinal thrombosis, and myocardial infarction. Additionally, cerebrovascular accidents (including cerebral infarction, cerebral hemorrhage and transient ischemic attacks) have been reported.

The reported risk of TVEs should be carefully weighed against the benefits to be derived from treatment with Epoetinum alfa particularly in patients with pre-existing risk factors.

In all patients, hemoglobin concentration should be closely monitored due to a potential increased risk of thromboembolic events and fatal outcomes when patients are treated at hemoglobin concentrations above the range for the indication of use.

The safety and efficacy of Epoetinum alfa therapy have not been established in patients with underly-
ing hematologic diseases (e.g. hemolytic anemia, sickle cell anemia, thalassemia).

There may be a moderate dose-dependent rise in the platelet count, within the normal range, during treatment with Epoetinum alfa. This regresses during the course of continued therapy. In addition, thrombocythemia above the normal range has been reported. It is recommended that the platelet count should be regularly monitored during the first 8 weeks of therapy.

Other causes of anemia (iron, folate or Vitamin B₁₂ deficiency, aluminum intoxication, infection or inflammation, blood loss, hemolysis and bone marrow fibrosis of any origin) should be evaluated and treated prior to initiating therapy with EPREX®, and when deciding to increase the dose. In most cases, the ferritin values in the serum fall simultaneously with the rise in packed cell volume. In order to ensure optimum response to Epoetinum alfa, adequate iron stores should be assured and iron supplementation should be administered if necessary:

- For chronic renal failure patients, iron supplementation (elemental iron 200-300 mg/day orally for adults and 100-200 mg/day orally for pediatrics) is recommended if serum ferritin levels are below 100 ng/mL.
- For cancer patients, iron supplementation (elemental iron 200-300 mg/day orally) is recommended if transferring saturation is below 20%.
- For patients in an autologous predonation program, iron supplementation (elemental iron 200 mg/day orally) should be administered several weeks prior to initiating the autologous predonos in order to achieve high iron stores prior to starting EPREX® therapy, and throughout the course of therapy.
- For patients scheduled for major elective orthopedic surgery, iron supplementation (elemental iron 200 mg/day orally) should be administered throughout the course of therapy with EPREX®. If possible, iron supplementation should be initiated prior to starting therapy with EPREX® to achieve adequate iron stores.

Very rarely, the initial presentation or exacerbation of porphyria has been observed in patients treated with EPREX®. EPREX® should be used with caution in patients with porphyria.

Erythropoiesis-stimulating agents (ESAs) are not necessarily equivalent. Therefore, it should be emphasized that patients should only be switched from one ESA (such as EPREX®) to another ESA with the authorization of the treating physician.

**Pure Red Cell Aplasia**

Antibody-mediated pure red cell aplasia (PRCA) has been very rarely reported after months to years of subcutaneous Epoetin treatment in chronic renal failure patients.

Cases also have been rarely reported in patients with hepatitis C treated with interferon and ribavirin, when ESAs are used concomitantly. ESAs are not approved in the management of anemia associated with hepatitis C.

In chronic renal failure patients developing sudden lack of efficacy, defined by a decrease in hemoglobin (1 to 2 g/dL per month) with increased need for transfusions, a reticulocyte count should be obtained and typical causes of non-response (e.g., iron folate or Vitamin B₁₂ deficiency, aluminum intoxication, infection or inflammation, blood loss, hemolysis and bone marrow fibrosis of any origin) should be investigated. If the reticulocyte count corrected for anemia (i.e., the reticulocyte “index”) is low (<20000/mm³ or <20000/μL or <0.5%) platelet and white blood cell counts are normal, and if no other cause of loss of effect has been found, anti-erythropoietin antibodies should be determined and a bone marrow examination should be considered for diagnosis of PRCA.

If anti-erythropoietin, antibody-mediated PRCA is suspected, therapy with EPREX® should be discontinued immediately. No other ESA therapy should be commenced because of the risk of cross-reaction. Appropriate therapy, such as blood transfusions, may be given to patients when indicated.
**Renal Failure Patients**

*Treatment of symptomatic anemia in adult and pediatric chronic renal failure patients*

Chronic renal failure patients being treated with EPREX® should have hemoglobin levels measured on a regular basis until a stable level is achieved, and periodically thereafter.

In chronic renal failure patients the rate of increase in hemoglobin should be approximately 1 g/dL (0.62 mmol/L)/per month and should not exceed 2 g/dL (1.2 mmol/L)/per month to minimize risks of an increase in hypertension. Dose should be reduced when hemoglobin approaches 12 g/dL.

In patients with chronic renal failure, maintenance hemoglobin concentration should not exceed the upper limit of the hemoglobin concentration range as recommended under Dosage and Administration. Hemoglobin levels targeted to 13 g/dL or higher may be associated with a higher risk of cardiovascular events, including death.

Some patients with more extended dosing intervals (greater than once weekly) of epoetin alfa may not maintain adequate hemoglobin levels (see Pharmacodynamic Properties) and may require an increase in epoetin alfa dose. Hemoglobin levels should be monitored regularly.

Patients with chronic renal failure and insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular events and mortality than other patients.

Based on information available to date, the use of Epoetinum alfa in predialysis [end stage renal insufficiency] patients does not accelerate the rate of progression of renal insufficiency.

Shunt thromboses have occurred in hemodialysis patients, especially in those who have a tendency to hypotension or whose arteriovenous fistulae exhibit complications (e.g., stenoses, aneurisms, etc.) Early shunt revision and thrombosis prophylaxis by administration of acetylsalicylic acid, for example, is recommended in these patients.

Hyperkalemia has been observed in isolated cases, though causality has not been established. Serum electrolytes should be monitored in chronic renal failure patients. If an elevated or rising serum potassium level is detected, then in addition to the appropriate treatment of the hyperkalemia, consideration should be given to ceasing Epoetinum alfa administration until the serum potassium level has been corrected.

As a result of an increase in packed cell volume, hemodialysis patients receiving EPREX® frequently require an increase in heparin dose during dialysis. If heparinization is not optimal, occlusion of the dialysis system is possible.

In some female chronic renal failure patients, menarches have resumed following Epoetinum alfa therapy; the possibility of potential pregnancy should be discussed and the need for contraception evaluated.

**Cancer Patients**

Cancer patients on EPREX® should have hemoglobin levels measured on a regular basis until a stable level is achieved and periodically thereafter.

ESAs are growth factors that primarily stimulate red blood cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumor cells. As with all growth factors, there is a concern that ESAs could stimulate the growth of tumors.

In controlled clinical studies, use of Epoetinum alfa and other ESAs have shown:

- decreased loco-regional control in patients with advanced head and neck cancer receiving radiation therapy when administered to a hemoglobin target of greater than 14 g/dl (8.7 mmol/L),
- shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to a hemoglobin target of 12-14 g/dl (7.5-8.7 mmol/L),
- Another ESA (darbepoietin alfa) increased risk of death when administered to target a hemoglobin of 12 g/dl (7.5 mmol/L) in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for use in this patient population.

In view of the above, the decision to administer recombinant erythropoietin treatment should be...
The use of EPREX® is not recommended in perisurgery patients with a baseline hemoglobin of >13 g/dL (8.1 mmol/L).

Interactions
No evidence exists that indicates that treatment with Epoetinum alfa alters the metabolism of other drugs. Drugs that decrease erythropoiesis may decrease the response to Epoetinum alfa.

Since cyclosporin is bound by red blood cells there is potential for a drug interaction. If EPREX® is given concomitantly with cyclosporin, blood levels of cyclosporin should be monitored and the dose of cyclosporin adjusted as the hematocrit rises.

No evidence exists that indicates an interaction between Epoetinum alfa and G-CSF or GM-CSF with regard to hematological differentiation or proliferation of tumor cells from biopsy specimens in vitro.

In patients with metastatic breast cancer, subcutaneous co-administration of 40000 IU/mL EPREX® with trastuzumab (6 mg/kg) had no effect on the pharmacokinetics of trastuzumab.

Pregnancy, Breast-feeding and Fertility
Use During Pregnancy
In animal studies, Epoetinum alfa has been shown to decrease fetal body weight, delay ossification and increase fetal mortality when given in weekly doses of approximately 20 times the recommended human weekly dose. These changes are interpreted as being secondary to decreased maternal body weight gain.

There are no adequate and well-controlled studies in pregnant women.

Epoetinum alfa should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (See Non-Clinical Information - Reproduction Toxicology).

Use During Lactation
Erythropoietin is present in human milk. However, it is not known whether Epoetinum alfa is distributed into human milk. Epoetinum alfa should be used with caution in nursing women.

In pregnant or lactating surgical patients participating in an autologous blood predonation program, the use of EPREX® is not recommended.
Hypersensitivity reactions, including cases of rash (including urticaria), anaphylactic reaction, and angioedema have been reported. Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have occurred also during Epoetinum alfa treatment in patients with previously normal or low blood pressure. Particular attention should be paid to sudden stabbing migraine-like headaches as a possible warning signal.

Effects on Fertility
In preclinical studies, intravenous administration of Epoetinum alfa caused a slight but not statistically significant decrease in fertility at 500 IU/kg, and increased pre- and post-implantation loss.

Effects on Ability to Drive and Use Machines
No studies on the effects of Epoetinum alfa on the ability to drive and use machines have been performed.

Adverse Reactions
Summary of the Safety Profile
The most frequent adverse drug reaction during treatment with Epoetinum alfa is a dose-dependent increase in blood pressure or aggravation of existing hypertension. Monitoring of the blood pressure should be performed, particularly at the start of therapy.

The most frequently occurring adverse drug reactions observed in clinical trials of Epoetinum alfa are diarrhea, nausea, vomiting, pyrexia, and headache. Influenza-like illness may occur especially at the start of treatment.

Respiratory tract congestion, which includes events of upper respiratory tract congestion, nasal congestion and nasopharyngitis, have been reported in studies with extended interval dosing in adult patients with renal insufficiency not yet undergoing dialysis.

An increased incidence of thrombotic vascular events (TVEs), has been observed in patients receiving ESAs (See Warnings and Precautions).

Clinical Trial Experience
Of a total 3559 subjects in 27 randomized, double-blinded, placebo or standard of care controlled studies, the overall safety profile of Epoetinum alfa was evaluated in 2136 anemic subjects. Included were 228 Epoetinum alfa-treated CRF subjects in 4 chronic renal failure studies (2 studies in predialysis [N=131 exposed CRF subjects not yet on dialysis] and 2 in dialysis [N=97 exposed CRF subjects on dialysis]); 1404 exposed cancer subjects in 16 studies of anemia due to chemotherapy; 144 exposed subjects in 4 HIV-infection studies; 147 exposed subjects in 2 studies for autologous blood donation; and 213 exposed subjects in 1 study in the perisurgical setting. Adverse drug reactions reported by 1% of subjects treated with Epoetinum alfa in these trials are shown in the table below:

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Adverse Drug Reaction</th>
<th>Predialysis</th>
<th>Dialysis</th>
<th>Oncology</th>
<th>HIV</th>
<th>ABD</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>EPO Placebo</td>
<td>EPO Placebo</td>
<td>EPO Non-ESA</td>
<td>EPO Placebo</td>
<td>EPO Non-ESA</td>
<td>EPO Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N=131 n (%)</td>
<td>N=97 n (%)</td>
<td>N=46 n (%)</td>
<td>N=1404 n (%)</td>
<td>N=930 n (%)</td>
<td>N=144 n (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>14 (11)</td>
<td>10 (13)</td>
<td>23 (24)</td>
<td>13 (28)</td>
<td>265 (19)</td>
<td>193 (21)</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>16 (12)</td>
<td>8 (10)</td>
<td>7 (7)</td>
<td>4 (9)</td>
<td>168 (12)</td>
<td>102 (11)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>12 (9)</td>
<td>6 (8)</td>
<td>9 (9)</td>
<td>8 (17)</td>
<td>173 (12)</td>
<td>134 (14)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Chills</td>
<td>6 (5)</td>
<td>2 (3)</td>
<td>10 (10)</td>
<td>3 (7)</td>
<td>33 (2)</td>
<td>32 (3)</td>
</tr>
<tr>
<td></td>
<td>Influenza like illness</td>
<td>1 (1)</td>
<td>NR</td>
<td>9 (9)</td>
<td>6 (13)</td>
<td>23 (2)</td>
<td>10 (1)</td>
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<tr>
<td></td>
<td>Injection site reaction</td>
<td>14 (11)</td>
<td>16 (20)</td>
<td>1 (1)</td>
<td>NR</td>
<td>42 (3)</td>
<td>31 (3)</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>4 (3)</td>
<td>4 (5)</td>
<td>9 (9)</td>
<td>6 (13)</td>
<td>189 (13)</td>
<td>130 (14)</td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
<td>9 (7)</td>
<td>10 (13)</td>
<td>NR</td>
<td>NR</td>
<td>72 (5)</td>
<td>34 (4)</td>
</tr>
</tbody>
</table>
### Overdose

The therapeutic margin of Epoetinum alfa is very wide. Overdosage of Epoetinum alfa may produce effects that are extensions of the pharmacological effects of the hormone. Phlebotomy may be performed if excessively high hemoglobin levels occur. Additional supportive care should be provided as necessary.

### Pharmacological Properties

#### Pharmacodynamic Properties

Erythropoietin (EPO) is a glycoprotein hormone produced primarily by the kidney in response to hypoxia and is the key regulator of red blood cell (RBC) production. EPO is involved in all phases of erythropoiesis, and has its principal effect...
the level of erythroid precursors. After EPO binds to its cell surface receptor, it activates signal transduction pathways that interfere with apoptosis and stimulates erythroid cell proliferation. Recombinant human EPO (Epoetinum alfa), expressed in Chinese hamster ovary cells, has a 165 amino acid sequence identical to that of human urinary EPO; the 2 are indistinguishable on the basis of functional assays. The apparent molecular weight of erythropoietin is 32000 to 40000 dalton.

Pharmacodynamic responses to HSA-free Epoetinum alfa, change in percent reticulocytes, hemoglobin, and total red blood cell counts as well as the area under the curve (AUCs) of these pharmacodynamic parameters, were similar between two dosing regimens (150 IU/kg SC three times per week to 40000 IU/mL SC once weekly).

ESAs are growth factors that primarily stimulate red cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumor cells.

**Clinical efficacy and safety**

**Chronic renal failure**

Epoetinum alfa has been studied in clinical trials in adult anemic CRF patients, including patients on dialysis and patients not yet on dialysis, to treat anemia and maintain hematocrit within a concentration range of 30-36%.

In clinical trials at starting doses of 50-150 IU/kg three times per week, approximately 95% of all patients responded with a clinically significant increase in hematocrit. After approximately two months of therapy, virtually all patients were transfusion-independent. Once the hematocrit concentration range was achieved, the maintenance dose was individualized for each patient.

In the three largest clinical trials conducted in adult patients on dialysis, the median maintenance dose necessary to maintain the hematocrit between 30-36% was approximately 75 IU/kg given three times per week.

In a double-blind, placebo-controlled, multicenter, quality of life study in CRF patients on hemodialysis, clinically and statistically significant improvement was shown in the patients treated with Epoetinum alfa compared to the placebo group when measuring fatigue, physical symptoms, relationships and depression (Kidney Disease Questionnaire) after six months of therapy. Patients from the group treated with Epoetinum alfa were also enrolled in an open-label extension study which demonstrated improvements in their quality of life were maintained for an additional 12 months.

**Adult patients with renal insufficiency not yet undergoing dialysis**

In clinical trials conducted in patients with CRF not on dialysis treated with Epoetinum alfa, the average duration of therapy was nearly five months. These patients responded to Epoetinum alfa therapy in a manner similar to that observed in patients on dialysis. Patients with CRF not on dialysis demonstrated a dose-dependent and sustained increase in hematocrit when Epoetinum alfa was administered by either an intravenous or subcutaneous route. Similar rates of rise of hematocrit were noted when Epoetinum alfa was administered by either route. Moreover, Epoetinum alfa doses of 75-150 IU/kg per week have been shown to maintain hematocrits of 36-38% for up to six months.

In a study with extended interval maintenance dosing of EPREX® (once weekly, once every 2 weeks, and once every 4 weeks) some patients with longer dosing intervals did not maintain adequate hemoglobin levels and reached protocol-defined hemoglobin withdrawal criteria (0% in once weekly, 3.7% in once-every-2-weeks, and 3.3% in the once-every-4-weeks groups).

A randomized prospective trial (CHOIR) evaluated 1432 anemic chronic renal failure patients who were not undergoing dialysis. Patients were assigned to Epoetinum alfa treatment targeting a maintenance hemoglobin level of 13.5 g/dL (higher than the recommended target hemoglobin level) or 11.3 g/dL. A major cardiovascular event (death, myocardial infarction, stroke or hospitalization for congestive heart failure) occurred among 125 (18%) of the 715
patients in the higher hemoglobin group compared to 97 (14%) among the 717 patients in the lower hemoglobin group (hazard ratio [HR] 1.3, 95% CI: 1.0, 1.7, p = 0.03).

**Treatment of patients with chemotherapy-induced anemia**

Epoetinum alfa has been studied in clinical trials in adult anemic cancer patients with lymphoid and solid tumors, and patients on various chemotherapy regimens, including platinum and non-platinum-containing regimens. In these trials, Epoetinum alfa administered three times a week (t.i.w.) and once weekly has been shown to increase hemoglobin and decrease transfusion requirements after the first month of therapy in anemic cancer patients. In some studies, the double-blind phase was followed by an open-label phase during which all patients received Epoetinum alfa and a maintenance of effect was observed.

Available evidence suggests the hematopoietic response to Epoetinum alfa therapy is similar between patients with non-myeloid hematologic and solid tumors and in patients with or without tumor bone marrow infiltration. Comparable intensity of chemotherapy in the Epoetinum alfa and placebo groups in the chemotherapy trials was demonstrated by a similar area under the neutrophil time curve in patients treated with Epoetinum alfa and placebo-treated patients, as well as by a similar proportion of patients in groups treated with Epoetinum alfa and placebo-treated groups whose absolute neutrophil counts fell below 1000 and 500 cells/μL.

In a prospective, randomized, double-blind, placebo-controlled trial conducted in 375 anemic patients with various non-myeloid malignancies receiving non-platinum chemotherapy, there was a significant reduction of anemia-related sequelae (e.g. fatigue, decreased energy, and activity reduction), as measured by the following instruments and scales: Functional Assessment of Cancer Therapy-Anemia (FACT-An) general scale, FACT-An fatigue scale, and Cancer Linear Analogue Scale (CLAS).

The totality of evidence, including results of meta-analyses and clinical experience from controlled studies of ESAs in patients with cancer, continues to support a favorable benefit-risk balance for the use of ESAs in patients with chemotherapy-induced anemia, when used according to the prescribing information. In meta-analyses of studies in which patients were receiving chemotherapy there were no statistically significant increases in either mortality or tumor progression. Signals in individual studies conducted outside of the recommendations in the product labeling (hemoglobin targets above 12 g/dL and/or no chemotherapy treatment) have raised concerns (see Warnings and Precautions – Cancer Patients).

**Pharmacokinetic Properties**

**Intravenous Administration**

Measurement of Epoetinum alfa following multiple dose intravenous (IV) administration of 50 to 100 IU/kg revealed a half-life of approximately 4 hours in healthy subjects and a longer half-life in renal failure patients of approximately 5 hours after doses of 50, 100 and 150 IU/kg. A half-life of approximately 6 hours has been reported in children. With at least 4 days of PK blood sampling, half-life estimates ranging from 20.1 to 33.0 hours were observed in cancer subjects receiving 667 and 1500 IU/kg IV doses of Epoetinum alfa.

**Subcutaneous Administration**

Serum concentrations following subcutaneous injection are lower than those following intravenous injection. Serum levels increase slowly and reach a peak 12 to 18 hours after subcutaneous dosing. The peak serum concentration is below the peak observed using the intravenous route (approximately 1/20th of the value). There is no accumulation: serum levels remain the same, whether data are collected 24 hours after subcutaneous dosing. The peak serum concentration is below the peak observed using the intravenous route (approximately 1/20th of the value).

In a prospective, randomized, double-blind, placebo-controlled trial conducted in 375 anemic patients with various non-myeloid malignancies receiving non-platinum chemotherapy, there was a significant reduction of anemia-related sequelae (e.g. fatigue, decreased energy, and activity reduction), as measured by the following instruments and scales: Functional Assessment of Cancer Therapy-Anemia (FACT-An) general scale, FACT-An fatigue scale, and Cancer Linear Analogue Scale (CLAS). The half-life for the subcutaneous route of administration is approximately 24 hours. Mean half-life values in healthy subjects were 19.4 ± 8.1 and 15.0 ± 6.1 with multiple dosing of 150 IU/kg three times per week and 40000 IU/mL once weekly, respectively.
In a study comparing 40000 IU SC once weekly to 150 IU/kg SC three times per week dosing regimens of HSA-containing Epochen alfa in healthy subjects, the following parameters were estimated using data corrected for predose endogenous erythropoietin concentration during Week 4:

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
<th>C_{\text{max}} (mIU/mL)</th>
<th>C_{\text{min}} (mIU/mL)</th>
<th>t(^\frac{1}{2}) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 IU/kg TIW</td>
<td>191 (100.1)</td>
<td>39 (17.9)</td>
<td>31.8</td>
</tr>
<tr>
<td>(n=24)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40000 IU QW</td>
<td>785 (427.3)</td>
<td>13 (9.5)</td>
<td>39.3</td>
</tr>
<tr>
<td>(n=22)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TIW = three times per week  
QW = once weekly  
Data from Study PHI 370

Based on AUC comparison, relative bioavailability of Epochen alfa 40000 IU once weekly versus 150 IU/kg three times per week was 176%.

In a study comparing 40000 IU SC once weekly versus 150 IU/kg SC three times per week dosing of HSA-free Epochen alfa in healthy subjects, the following parameters were estimated using data corrected for predose endogenous erythropoietin concentration during Week 4:

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
<th>C_{\text{max}} (mIU/mL)</th>
<th>C_{\text{min}} (mIU/mL)</th>
<th>t(^\frac{1}{2}) (h)</th>
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<tr>
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<td>(n=22)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TIW = three times per week  
QW = once weekly  
Data from Study PHI 370

Based on AUC comparison, relative bioavailability of Epochen alfa 40000 IU/mL once weekly versus 150 IU/kg three times per week was 239%.

The bioavailability of subcutaneous Epochen alfa after a dose of 120 IU/kg is much lower than that of the intravenous drug: approximately 20%.

Pharmacokinetic parameters were estimated in healthy subjects and anemic cancer subjects receiving cyclic chemotherapy and either 150 IU/kg three times per week or 40000 IU/mL once weekly of HSA-containing Epochen alfa. The pharmacokinetic parameters of anemic cancer subjects were different from those observed in healthy subjects during Week 1 (when the anemic cancer subjects were receiving chemotherapy) but were similar during Week 3 (when the anemic cancer subjects were not receiving chemotherapy).

Pharmacokinetics of HSA-free Epochen alfa were studied in anemic cancer subjects receiving cyclic chemotherapy after the 150 IU/kg three times per week and 40000 IU/mL once weekly dosing regimens. In general, there was a high degree of variability associated with the pharmacokinetic parameters in anemic cancer subjects. In general, the first pharmacokinetic profile of Epochen alfa during Week 1 (when the anemic cancer subjects were receiving chemotherapy) demonstrated higher C_{\text{max}} increased half-life, and lower clearance than the second pharmacokinetic profile during Week 3 or 4 (when the anemic cancer subjects were not receiving chemotherapy).
Reproduction Toxicology

Preclinical studies have shown no evidence of teratogenicity in rats or rabbits at dosages up to 500 IU/kg/day administered intravenously. However, intravenous administration of Epoetinum alfa causes a slight but not statistically significant decrease in fertility at 500 IU/kg, increased pre- and post-implantation loss and decreased fetal body weight at 100 and 500 IU/kg/day, and delayed ossification at 20, 100, and 500 IU/kg/day. The latter finding was associated with reduced maternal body weight. Intravenous administration to lactating rats resulted in decreases in body weight gain, delays in appearance of abdominal hair and eyelid opening, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 IU/kg/day group. There were no Epoetinum alfa-related effects on the F2 generation fetuses.

NON-CLINICAL INFORMATION

Preclinical Safety Data

Chronic Toxicity

In some pre-clinical toxicological studies in dogs and rats, but not in monkeys, Epoetinum alfa therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of chronic renal failure in humans; it may be related to secondary hyperparathyroidism or unknown factors. In one study, there was no difference in the incidence of bone marrow fibrosis in hemodialysis patients treated with Epoetinum alfa for 3 years and hemodialysis patients not treated with Epoetinum alfa.

Carcinogenicity

Long-term carcinogenicity studies have not been carried out. There are conflicting reports in the literature regarding ESAs as tumor proliferators. The clinical significance of these reports, based on in vitro findings from human tumor samples, is unknown.

Mutagenicity

Epoetinum alfa does not induce bacterial gene mutation (Ames Test), chromosomal aberrations in mammalian cells, micronuclei in mice, or gene mutation at the HGPRT locus.

<table>
<thead>
<tr>
<th></th>
<th>C_{max} (mIU/mL)</th>
<th>C_{min} (mIU/mL)</th>
<th>t_{max} (h)</th>
<th>t_{1/2} (h)</th>
<th>CL/F (mL/h/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 1 when subjects were receiving chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 IU/kg TIW (n=16)</td>
<td>642 (402.7)</td>
<td>207 (301.4)</td>
<td>14.98 (8.8)</td>
<td>28.3 (19.2)</td>
<td>12.1 (11.2)</td>
</tr>
<tr>
<td>40000 IU QW (n=19)</td>
<td>1289 (431.0)</td>
<td>148 (144.2)</td>
<td>48.74 (283)</td>
<td>76.2 (45.8)</td>
<td>5.6 (1.8)</td>
</tr>
<tr>
<td><strong>Week 3 or 4 when subjects were not receiving chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 IU/kg TIW (n=9)</td>
<td>357 (246.2)</td>
<td>---</td>
<td>20.67 (20.1)</td>
<td>30.0 (10.0)</td>
<td>17.2 (7.8)</td>
</tr>
<tr>
<td>40000 IU QW (n=11)</td>
<td>941 (372.7)</td>
<td>---</td>
<td>24.54 (10.8)</td>
<td>46.7 (22.3)</td>
<td>12.7 (7.5)</td>
</tr>
</tbody>
</table>

TIW = three times per week
QW = once weekly
Data from Study EPO-P01-108

a “n” as indicated unless specifically stated
b C_{min} was estimated by averaging weekly predose serum concentrations during the study

PHARMACEUTICAL INFORMATION

List of Excipients

HSA-free, Phosphate-buffered, Pre-filled Syringes with needle guard (PROTECS)


Incompatibilities

Do not dilute or transfer to any other container. Do not administer by intravenous infusion or in conjunction with other drug solutions.

Shelf Life

See expiry date on the outer pack.

Storage Conditions

EPREX® syringes are to be stored between 2°C and 8°C [36°F to 46°F] in the refrigerator, away from the freezer compartment. Do not freeze or shake. Keep the syringes in the original carton to protect from light. EPREX® syringes that are being used or about to be used can be kept at room temperature (not above 25°C) for a maximum single period of 7 days. Keep out of the sight and reach of children.
**Nature and Contents of Container**

EPREX® is supplied in type I glass prefilled syringes with FluroTec®-coated rubber stoppers.

The pre-filled syringes are fitted with the PROTECS™ needle guard device to help prevent needle stick injuries after use.

Package of 6 syringes
1000 IU/0.5 mL of Epoetinum alfa
2000 IU/0.5 mL of Epoetinum alfa
3000 IU/0.3 mL of Epoetinum alfa
4000 IU/0.4 mL of Epoetinum alfa
5000 IU/0.5 mL of Epoetinum alfa
6000 IU/0.6 mL of Epoetinum alfa
8000 IU/0.8 mL of Epoetinum alfa
10000 IU/1.0 mL of Epoetinum alfa
1 syringe per package
20000 IU/0.5 mL of Epoetinum alfa
30000 IU/0.75 mL of Epoetinum alfa
40000 IU/1.0 mL of Epoetinum alfa

**Instructions for Use and Handling**

[The product is for single use only.]

The product should not be used, and should be discarded if:
- the seal is broken,
- the liquid is colored or particles are in it,
- it may have been frozen,
- or there has been a refrigeration failure.

**Patient Instructions for Use and Handling**

*Injecting EPREX® under the skin yourself*

At the start of your therapy, EPREX® may be injected by medical or nursing staff. However, your doctor may decide that it is right for you to learn how to inject EPREX® under the skin (subcutaneously) yourself. You will receive appropriate training for you to do this. Under no circumstances should you attempt to inject yourself unless you have been trained to do so.

If EPREX® is injected under the skin (subcutaneously), the amount injected is not normally more than one milliliter (1 mL) in a single injection.

EPREX® is given alone and not mixed with other liquids for injection.

Do not shake EPREX® syringes. Prolonged vigorous shaking may damage the product. If the product has been shaken vigorously, don’t use it.

*How to inject yourself using a pre-filled syringe*

The pre-filled syringes are fitted with the PROTECS™ needle guard device to help prevent needle stick injuries after use. This is indicated on the packaging.

- **Take a syringe out of the refrigerator.** The liquid needs to come to room temperature. This usually takes between 15 to 30 minutes.
- **Check the syringe,** to make sure it is the right dose, has not passed its expiry date, is not damaged, and the liquid is clear and not frozen.
- **Choose an injection site.** Good sites are the top of the thigh and around the tummy (abdomen) but away from the navel. Vary the site from day to day.
- **Wash your hands.** Use an antiseptic swab on the injection site, to disinfect it.
- **Take the cover off the syringe** by holding the barrel and pulling the cover off carefully without twisting it. Don’t push the plunger, touch the needle or shake the syringe.
- **Pinch a fold of skin** between your thumb and index finger. Don’t squeeze it.
- **Push the needle in fully.** Your doctor or nurse may have shown you how to do this.
- **Check that you haven’t punctured a blood vessel.** Pull back slightly on the plunger. If you see blood, take the syringe out and try somewhere else.
- **Push the plunger with your thumb** as far as it will go to inject all of the liquid. Push it slowly and evenly, keeping the skinfold pinched. The needle guard will not activate unless the entire dose is given.
- **When the plunger is pushed as far as it will go,** take out the needle and let go of the skin.
- **Take your thumb off the plunger.** Allow the syringe to move up until the entire needle is covered by the needle guard.
- **Press an antiseptic swab** over the injection site for a few seconds after the injection.
- **Dispose of your used syringe** in a safe container. Only take one dose of EPREX® from each syringe. If any liquid remains in the syringe after an injection, the syringe should be properly disposed of, not reused. (See ‘Instructions for Disposal.’)

*What to do if you use too much EPREX®*
Tell the doctor or nurse immediately if you think too much EPREX® has been injected.

*What to do if you forget to use EPREX®*
Make the next injection as soon as you remember. If you are within a day of your next injection, forget the missed one and carry on with your normal schedule. Do not double up the injections.

*How should EPREX® be stored?*
In hospital, pre-filled syringes are stored unopened in a refrigerator between 2 and 8 degrees centigrade. If you are using EPREX® at home, it is important that the pre-filled syringe is stored in your refrigerator although not in the freezer compartment. EPREX® should not be frozen. Allow the pre-filled syringe to reach room temperature prior to using it. This usually takes between 15 and 30 minutes. EPREX® pre-filled syringes that are being used or about to be used can be kept at room temperature (not above 25°C) for a maximum single period of 7 days. Pre-filled syringes should be protected from light.

*Other important points*
EPREX® should not be used:
- after the expiry date on the label;
- if the seal is broken,
- if the liquid is colored or you can see particles floating in it;
- if you know, or think that it may have been accidentally frozen;
- if there has been a refrigerator failure;
Always keep medicine out of the reach of children.

*Instructions for Disposal*
Any unused product or waste material should be disposed of in accordance with local requirements. Medicines should not be disposed of via waste water or in household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

**MANUFACTURED BY**
See outer carton.

**DATE OF REVISION OF THE TEXT**
08-March-2013 based on CCDS 20-December-2012