PACKAGE LEAFLET: INFORMATION FOR THE USER

EPOPLUS 2000 IU/ml vial containing solution for S.C./I.V. injection

For intravenous or subcutaneous use.

- **Drug substance:** Each 1 mL vial contains 2000 IU epoetin alpha (recombinant human erythropoietin).

- **Excipients:** Human albumin, sodium citrate, sodium chloride, citric acid, polysorbate 20 and water for injection

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Read all of this leaflet carefully before you start using this medicine because it contains important information.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others.
- If you visit to the doctor or hospital tell your doctor about using this medicine.
- Follow the instructions on this leaflet. Do not use higher or lower doses than the recommended dose for this medicine.

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1. What EPOPLUS is and what it is used for
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1. What EPOPLUS is and what it is used for

EPOPLUS is a clear and colorless solution for subcutaneous or intravenous injection. It contains a hormone called epoetin (erythropoietin) which promotes the formation of red blood cells.

Epoetin alpha is produced with a special genetic technology and acts in the same way with natural erythropoietin hormone.

EPOPLUS is marketed in vials containing clear, colorless solution for injection.

EPOPLUS contains 2000 IU epoetin alpha per mL. Each carton contains 5, 6 or 10 vials.

EPOPLUS is used
- for the treatment of anemia due to chronic renal failure (renal anemia) in patients undergoing dialysis (procedure for cleaning blood) or patients not yet undergoing dialysis,

- for increasing or maintaining the blood level of red cells (erythrocytes), and to reduce the need of blood transfusions in such patients.
2. Before you use EPOLUS

If any of these warnings apply to you even in the past, please tell your doctor.

DO NOT use EPOPLUS

- If you have hypersensitivity to erythropoietin, including human serum albumin and/or to any of the excipients in this medicinal product,
- If you have uncontrolled hypertension,
- If you cannot receive adequate pre-medication for any reason, that protects you from clotting of blood,
- If you have pure red cell aplasia (a condition in which the production of red blood cells decreases or stops) due to treatment with any erythropoietin preparation,
- If you have cancer and cancer-related anemia, and anemia associated with chemotherapy for cancer.

USE WITH CAUTION

If you or your child have any of the following;
- Epileptic seizures,
- Liver disease,
- Anemia caused by other reasons,
- Heart disease (e.g. angina),
- Circulatory disorders that cause tingling, cold hand feet problem or muscle cramps in legs,
- Blood clots / disorders of blood clotting,
- Kidney disease.

Before you start treatment with EPOPLUS;
- Red blood cell production was decreased or stopped (Pure Red Cell Aplasia) in some of the patients who were treated with agents stimulating the formation of blood, due to the development of antibodies against erythropoietin. If your doctor suspects or confirms that you have these antibodies in your blood, you must not be treated with EPOPLUS.
- It is not known whether EPOPLUS exerts a different effect in patients who have disorders associated with the presence of abnormal hemoglobin in red blood cells (hemoglobinopathies), severe liver disease, stroke or high platelet counts in blood. If any of these apply to you, your doctor will discuss with you and will need to exercise caution for your treatment.
During the treatment with EPOPLUS;

Since the risk of death, having heart attack, stroke and embolism is increased, and an influence for cancer worsening is present in cancer cases at hemoglobin levels of 11 g/dL or higher, your doctor will keep the hemoglobin concentration below a certain level in your blood and ensure that your hemoglobin level is above 10 g/dL, while administrating your drug at the possible lower dose in order to minimize the need for blood cell transfusion.

- Your doctor will check iron amounts in your blood before and during EPOPLUS treatment. If iron amounts are very low in your blood, your doctor may give additional treatment for iron deficiency.
- Your doctor will check your blood pressure before and during EPOPLUS treatment. If you have high blood pressure which cannot be controlled with medication or special diet, your doctor will stop EPOPLUS treatment or decrease your dose.
- If you feel exhausted, weak or experience dyspnea tell your doctor; these symptoms may mean that EPOPLUS treatment is inefficient.
- Your doctor will check other reasons for your anemia; he/she may perform blood tests or examine your bone marrow for this purpose. If you have developed “Pure Red Cell Aplasia”, your treatment with EPOPLUS will be discontinued as it would not be appropriate for you to take drugs stimulating blood formation such as EPOPLUS.

If any of these warnings apply to you even in the past, please tell your doctor.

**Taking EPOPLUS with food and drink**
EPOPLUS use is not influenced by food and drink. It may be administrated with or without food.

**Pregnancy**
*Ask your doctor or pharmacist before using this medicine.*

Since there is limited experience on EPOPLUS use during pregnancy, it is at your doctor’s discretion.

If you realize that you are pregnant during your treatment, tell your doctor or pharmacist immediately.

**Lactation**
*Ask your doctor or pharmacist before using this medicine.*

There is limited experience on EPOPLUS use during lactation.

Tell your doctor if you are breast feeding or planning to do so. Your doctor will advise you whether to stop or continue breast feeding, or to stop or continue your treatment.

**Driving and using machines**
If you have renal failure, you should exercise caution when performing potentially dangerous activities, such as driving and using machines until optimal maintenance dose for EPOPLUS is determined due to increased risk of hypertension during the beginning of EPOPLUS treatment.
**Important information regarding some of the excipients of EPOPLUS**

EPOPLUS contains 5.8 mg/mL sodium citrate and 5.8 mg/mL sodium chloride as excipients. This medicinal product contains less than 1 mmol sodium (23 mg) per mL; i.e. essentially “sodium-free”.

EPOPLUS contains human serum albumin as an excipient, and therefore has a risk of transmitting viral disease, although the risk is very low. Risk of carrying the disease called Creutzfeldt-Jacob is believed to be very low theoretically.

**Taking other medicines**  
If EPOPLUS is given concomitantly with medicines containing cyclosporine, a drug used for organ and tissue transplants or rheumatic diseases (e.g. Behçet’s disease, nephritic syndrome, psoriasis or atopic dermatitis), blood concentration of cyclosporine should be monitored.

When used concomitantly with blood forming drugs, the efficacy of EPOPLUS may be increased.

*Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.*

**3. How to use EPOPLUS**

**Instructions for appropriate use and dose/frequency:**  
When using EPOPLUS, strictly follow the instructions of your doctor all the time. If you are not sure, ask your doctor or pharmacist.

The dose of EPOPLUS depends on the settings of your disease, administration route (subcutaneous or intravenous) of the injection and your body weight.

- **Anemia due to chronic renal failure:**

Injection may be given subcutaneously or intravenously. In case of intravenous administration, the solution should be injected in at least 2 minutes. For example, in hemodialysis patients administration is done via arteriovenous fistulae at the end of dialysis.

In patients not undergoing hemodialysis, subcutaneous injection is usually given.

EPOPLUS is a two-step treatment:

a) **Correction of anemia**

- **Subcutaneous administration**

For subcutaneous injection, starting dose is 20 IU/kg body weight per injection 3 times a week.

After 4 weeks, your doctor will perform a test. If you have insufficient response to treatment, your dose may be increased to 40 IU/kg per injection 3 times a week. Your doctor may
continue increasing your dose with monthly intervals, if necessary. Additionally, weekly dose can be divided into daily doses.

For intravenous injection, starting dose is 40 IU/kg body weight per injection 3 times a week.

After 4 weeks, your doctor will perform a test. If you have insufficient response to treatment, your dose may be increased to 80 IU/kg per injection 3 times a week. Your doctor may continue increasing your dose with monthly intervals, if necessary.

Maximum dose should not exceed 720 IU/kg body weight for both methods of administration.

b) Maintenance of adequate level of red blood cells

Maintenance dose: Once your red blood cells reach an acceptable level, the dose of your drug is reduced by half of the dose used for correction of your anemia.

Your doctor will adjust your dose weekly or twice weekly in order to determine the maintenance dose for you.

EPOPLUS is a long-term treatment under normal circumstances. However, it can be interrupted at any time if necessary.

- In adults having myelodysplastic syndrome, a disease characterized with insufficient production of healthy blood cells by bone marrow:

Injections must be given by subcutaneous route.

If your hemoglobin level is 10 g/dL or less, your doctor may initiate EPOPLUS treatment. The recommended starting dose is 30,000 IU per week (corresponds approximately to 450 IU/kg body weight per week when based on a patient with average body weight). This can be divided into 3-7 doses per week. Your doctor will obtain blood samples routinely. He/she may increase or decrease your dose, or discontinue treatment depending on test results. Hemoglobin values should not exceed 11 g/dL. Maximum dose should not exceed 60,000 IU per week.

**Administration route and method:**
EPOPLUS should be initiated by experienced physicians for the indications mentioned above. It is recommended that the first dose must be administered under medical supervision since hypersensitivity reactions are observed in some of the cases.

EPOPLUS is administered by subcutaneous or intravenous route. In case of intravenous administration, the solution should be injected in at least 2 minutes.

If you are a pre-dialysis patient, you should always prefer subcutaneous route in order to avoid perfusion of peripheral veins. Maximum volume to be administered per injection site must be 1 mL. When greater volumes are required, multiple injection sites should be used. Injections must be given into extremities or anterior abdominal wall.
Different age groups:

Children:
Clinical studies in children demonstrated that in general, higher dose of EPOPLUS is required with decreasing age. However, the recommended dose schedule should be followed since individual response can not be predicted beforehand.

Clinical studies have been conducted in children and adolescents under the age of 18 with anemia due to chronic renal disease.

EPOPLUS should not be used in infants below the age of two years with anemia due to chronic renal disease.

Elderly:
Special dose adjustments for elderly patients have not been defined.

If you think the effect of EPOPLUS is too strong or too weak, talk to your doctor or pharmacist.

Use in special populations:

Renal failure:
Ask your doctor for dose adjustment.

Hepatic failure:
This medicinal product must be used with caution in patients with serious liver disease.

If you think the effect of EPOPLUS is too strong or too weak, talk to your doctor or pharmacist.

If you take more EPOPLUS than you should
If you take more EPOPLUS than you should, talk to your doctor or pharmacist.

The blood concentration margin required for safe treatment of EPOPLUS is very wide. No symptoms of poisoning were identified even at very high serum levels.

If you forget to use EPOPLUS
Take the next dose immediately and carry on at normal intervals as instructed by your doctor.

Do not administrate double dose to make up the missing dose.

Possible effects when EPOPLUS is discontinued
Do not discontinue EPOPLUS treatment until your doctor decides to do so.

4. Possible side effects
As with all medicines, individuals who are sensitive to ingredients of EPOPLUS can experience side effects. However, it does not mean everybody gets them.
Side effects are listed according to the following categories:

**Very common:** affects at least 1 in every 10 individual.
**Common:** affects less than 1 in every 10 individual but more than 1 in every 100 individual.
**Uncommon:** affects less than 1 in every 100 individual but more than 1 in every 1000 individual.
**Rare:** affects less than 1 in every 1000 individual but more than 1 in every 10.000 individual.
**Very rare:** affects less than 1 in every 10.000 individual.

**Common**
- Hypertension: If you are an adult or child hemodialysis patient or an adult undergoing peritoneal dialysis or a renal failure patient not yet undergoing dialysis, your blood pressure may increase dependent on dose or your current hypertension may worsen during EPOPLUS treatment. This increase in your blood pressure may be corrected by blood pressure lowering agents. Your blood pressure must be monitored especially at the initial phase of your treatment.

**Uncommon:**
- Headache (particularly if you have sudden, stabbing migraine-like headaches, tell your doctor).

**Rare:**
- Hypersensitivity reaction (severe allergic reaction which may result in abnormal breathing with wheezing or difficulty in breathing, swelling of face, tongue or throat, or swelling of the area near injection site or feeling dizzy, stupor or fainting).
- Very high blood pressure causing headache, particularly sudden and stabbing migraine-like headaches, confusion, speech impairment, crises and spasms.
- Skin rashes.

**Very rare:**
- Increased platelet counts.
- Insufficient blood supply to heart and brain, heart attack, cerebral hemorrhage, stroke, deep vein thrombosis, occlusion in lungs (pulmonary embolism), dilatation of the wall arteries (aneurism), blood clot formation in intraocular vessels and artificial kidney.
- Clots may occur (shunt thromboses) especially if you are susceptible to hypotension or have vascular disorders (arteriovenous fistula complication; e.g. stenosis, aneurism etc.). In this case, ask your doctor about precautions (e.g. aspirin administration) prior initiating your drug.

*If you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.*

**5. How to store EPOPLUS**

*Keep EPOPLUS out of the reach and sight of children and in its package.*

Store in refrigerator between 2°C and 8°C.

Do not freeze, do not vigorously shake and protect from light.
Keep in original package.

**Use in accordance with the expiry date.**

*Do not use EPOPLUS after the expiry date which is stated on the outer carton.*

Only clear, colorless solutions which are free of visible particles must be used.

*Do not use EPOPLUS if you notice defects on product and/or package.*

*EPOPLUS 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.*

**Marketing Authorization Holder:** HASBIOTECH İlaç San. ve Tic. A.Ş.  
Hacılar / Kayseri

**Manufacturer:**  Centro de Immunologia Molecular  
Havana / Cuba

*This leaflet was last approved in ./././.*

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**INFORMATION FOR HEALTHCARE PROVIDERS**

As with any injectable product, the solution must be checked for particulates and discoloration prior to administration of injection.

This medicinal product must not be administrated by intravenous infusion or after mixing with other drugs.

It must be administered by intravenous or subcutaneous injection.

**Intravenous injection:**  
Depending on the total dose, injection should be given in at least 1 to 5 minutes. A bolus injection may be given from available venous part on the dialysis line during dialysis, or the injection may be given after 10 mL isotonic sodium chloride is administered to clear the dialysis line at the end of the dialysis in hemodialysis patients.  
Slower injections must be preferred in patients who experience reactions as flu-like symptoms to the treatment.

**Subcutaneous injection:**  
Maximum volume to be administered per injection site must be 1 mL. When greater volumes are required, multiple injection sites should be used. Injections must be given into hips or anterior abdominal wall.