PATIENT PACKAGE INSERT
IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS
(PREPARATIONS) – 1986

The medicine is dispensed with a doctor's prescription only

Name and strength of the medicine

EPREX® 2,000
EPREX® 3,000
EPREX® 4,000
EPREX® 5,000
EPREX® 6,000
EPREX® 8,000
EPREX® 10,000
EPREX® 20,000
EPREX® 30,000
EPREX® 40,000

Active ingredient and its quantity per dosage unit:

Epoetin alfa 16.8 mcg (EPREX 2,000), 25.2 mcg (EPREX 3,000), 33.6 mcg (EPREX 4,000), 42 mcg (EPREX 5,000), 50.4 mcg (EPREX 6,000), 67.2 mcg (EPREX 8,000), 84 mcg (EPREX 10,000), 168 mcg (EPREX 20,000), 252 mcg (EPREX 30,000), 336 mcg (EPREX 40,000)

Inactive and allergenic ingredients in the preparation – see in section 2 "Important information about some of the ingredients of the medicine" and section 6 "Further Information".

Read the leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed for the treatment of your ailment. Do not pass it on to others. It may harm them, even if it seems to you that their ailment is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

- EPREX is a medicine intended for treatment of anemia in patients suffering from chronic renal failure. If you have kidney disease, you may have a shortage of red blood cells if your kidneys do not produce enough erythropoietin (which is necessary for red blood cell production). EPREX stimulates the bone marrow to produce red blood cells,
- The medicine is intended to treat anemia in cancer patients receiving chemotherapy,
- The medicine is intended to treat anemia in anemic patients who donate their own blood to themselves, in AIDS patients treated with zidovudine preparations,

- The medicine is intended to treat anemia in anemic patients about to undergo surgery.

Therapeutic group:

Preparations for treatment of anemia.
EPREX belongs to the group of preparations which stimulate the production of red blood cells by the bone marrow.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- You suffer from high blood pressure that is not controlled with medicinal treatment.
- You are sensitive (allergic) to the active ingredient or to any of the additional ingredients contained in the medicine (see section 6).
- You are due to undergo major orthopedic surgery (such as hip or knee surgery), and you:
  - are suffering, or have suffered in the past, from severe heart disease.
  - are suffering, or have suffered in the past, from disorders related to the veins and/or arteries.
  - have recently had a heart attack or stroke.
  - cannot receive treatment with anticoagulants,
    EPREX may not be suitable for you. While on treatment with EPREX, some patients require treatment to lower the risk of formation of blood clots. If you cannot take anticoagulants, you must not use EPREX.
- You have been diagnosed with a problem in production of red blood cells by the bone marrow – PRCA (pure red cell aplasia, inability to produce a sufficient amount of red blood cells in the bone marrow) following previous treatment with preparations that stimulate red blood cell production (including EPREX).
- Do not use EPREX as preparation for a blood transfusion for yourself if you cannot receive a self blood donation during or after surgery.

Special warnings regarding use of the medicine

EPREX and other medicines that stimulate red blood cell production may increase the risk of development of blood clots in all patients. The risk may be higher if you have other risk factors: if you have had blood clots in the past or if you are at increased risk of blood clots (e.g., if you are overweight, have diabetes, have heart disease or you are bedridden for a long time because of surgery or illness).

Before treatment with EPREX, tell the doctor:

- If you are suffering, or have suffered in the past, from:
  - high blood pressure.

- epileptic seizures or stroke.
- liver disease.
- anemia that is different than those described in section 1 "What is the medicine intended for?".
- porphyria (a rare blood system disorder).
- an allergy to latex. The needle cover of this preparation contains latex rubber which may cause severe allergic reactions in patients who are sensitive to latex. See section 4 "Side effects" for the signs of an allergic reaction.

- **If you suffer from chronic renal failure,** particularly if you are not responding well to EPREX, the doctor will check your blood EPREX level. The reason is that if you are not responding to treatment, repeated increases in EPREX dosage may increase the risk of heart or blood vessel problems and could increase risk of myocardial infarction, stroke and death.
- **If you have cancer,** you should be aware that agents that stimulate red blood cell production (like EPREX) may act as a growth factor and therefore, in theory, may accelerate the progression of the cancer. **Depending on your medical situation, the doctor may prefer to treat you via a blood transfusion.**
- **If you have cancer,** be aware that use of EPREX has been associated with shorter survival and a higher death rate in head and neck and metastatic breast cancer patients who are receiving chemotherapy.
- **Serious skin side effects** including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with epoetin treatment.

SJS/TEN can appear initially as reddish target-like spots or circular patches on the trunk usually with blisters at their center. Also, ulcers of the mouth, throat, nose, genitals and eyes (red and swollen eyes) can occur. These serious rashes are often preceded by fever and/or flu-like symptoms. The rashes may progress to widespread peeling of the skin and life-threatening complications.
If you develop a serious rash or another of these skin symptoms, stop taking EPREX, contact your doctor immediately or seek medical care immediately.

Exercise caution with other preparations that stimulate production of red blood cells

- EPREX is part of a group of preparations that are used to stimulate the production of red blood cells. If you are being treated with EPREX and you received another medicine from this group – please confirm with the doctor that you can take the other preparation.

Tests and follow-up

During the course of treatment, you will be routinely referred to do blood pressure tests.

Drug interactions:

If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. In particular, inform the doctor or pharmacist if you are taking:

- Ciclosporin – a medicine given to prevent transplant rejection (for example, after a kidney transplantation). Your doctor may instruct you to undergo blood tests to monitor the level of ciclosporin during the course of treatment with EPREX.
- Iron supplements and other preparations that stimulate production of red blood cells may increase the efficacy of EPREX. Consult the doctor and he/she will decide if you should take them.

It is important to always remind the attending doctor that you are being treated with EPREX.

- If you visit a hospital or any clinic or family doctor for treatment/consultation – tell the medical staff that you are being treated with EPREX, since EPREX can affect other treatments or laboratory test results.

Pregnancy and breastfeeding

If you are pregnant, planning to become pregnant during the course of treatment or are breastfeeding, consult the doctor before commencing treatment.

Important information about some of the ingredients of the medicine

EPREX contains sodium

The preparation EPREX contains less than 1 mmol (23 mg) sodium per dose and can be considered sodium-free.

EPREX contains polysorbate 80

This medicine contains a maximum of 0.30 mg of polysorbate 80 in each syringe, equivalent to a concentration of 0.30 mg/ml.

Polysorbate may cause allergic reactions. Tell your doctor if you or your child has any known allergies.

3. HOW SHOULD THE MEDICINE BE USED?

Always use the preparation according to the doctor's instructions.

Check with the doctor or pharmacist if you are uncertain about the preparation dosage and treatment regimen.

The dosage and treatment regimen will be determined by the doctor only.

EPREX can be injected into a vein or under the skin. The doctor will decide how the preparation is to be injected. The injections will generally be given by a doctor or nurse. Depending on the reason for treatment, certain people will be able to learn how to self-inject under the skin. Self-injection under the skin requires training by the doctor or nurse before you start self-injecting.

In any case, you must not use EPREX:

- After the expiry date that appears on the syringe and the package.
- If you know or suspect that the preparation has been frozen.
- If there was any problem with the refrigerator.

The dosage you take is based upon your body weight in kilograms. In addition, the cause of anemia is also a factor in deciding upon the correct dosage.

Patients with renal disease:

- The doctor will make sure that your hemoglobin level is maintained between 10-12 g/dl, as a high hemoglobin level may increase the risk of blood clot formation and death. In children, the hemoglobin level should be maintained between 5.9-11 g/dl.
- The usual starting dose of EPREX for adults or children is 50 international units (IU) per kilogram of body weight, given 3 times a week.
- For patients on peritoneal dialysis, injection frequency may be twice a week.
- EPREX is given by two possible types of injection to children and adults: injection into a vein or injection under the skin. Your doctor will decide on the type of injection.
- Your doctor will instruct you to undergo blood tests to check whether there has been an improvement in your condition. The doctor may decide to adjust the dosage. Adjusting the dosage will be done according to the doctor's instructions, usually every 4 weeks. Avoid an increase greater than 2 g/dl in hemoglobin levels for a period of 4 weeks.
- Once the anemia improves as desired, your doctor will continue to perform routine blood tests. The doctor may adjust the dosage again to maintain the desired response to treatment. Your doctor will use the lowest effective dosage of EPREX to control the symptoms of the anemia.
- If you do not respond adequately to EPREX, your doctor will check the dosage and will inform you if you need to change the dosage of EPREX.
- If the frequency of administration of the medicine is greater than once weekly, you may not be able to maintain appropriate hemoglobin levels and you may have to increase the dosage or frequency of administration.
- You may be given iron supplements before and during EPREX treatment to improve the effectiveness of the treatment.
- If you are undergoing dialysis treatment during treatment with EPREX, your dialysis treatment regimen may be slightly adjusted. Your doctor will decide on this.

Cancer patients:

- The doctor will most likely initiate treatment with EPREX when your hemoglobin level is 10 g/dl or less.
- The doctor will make sure that your hemoglobin level is maintained between 10-

12 g/dl, as a high hemoglobin level may increase the risk of blood clot formation and death.

- The starting dose is **150 IU** per kilogram body weight, administered 3 times a week, or **450 IU** per kilogram body weight, once a week.
- The preparation will be given by injection under the skin.
- Your doctor will order blood tests to check whether your anemia is responding to treatment and will adjust the dosage as needed.
- You may be given iron supplements before and during EPREX treatment to improve the effectiveness of the treatment.
- You will usually continue EPREX treatment for one additional month after the end of chemotherapy in accordance with the doctor's instructions.

Patients donating their own blood for themselves:

- The usual dose is **600 IU** per kilogram body weight, administered twice a week.
- You may be given iron supplements before and during EPREX treatment to improve the effectiveness of the treatment.
- The preparation will be given through a vein, immediately after blood withdrawal, for 3 weeks before the surgery.

AIDS patients being treated with zidovudine:

The doctor may perform a blood test before starting the treatment to check erythropoietin blood levels. The dosage will be determined by the doctor for each patient independently, to achieve an adequate hemoglobin level (but not above 12 g/dl) to avoid the need for blood units.

Patients scheduled for major orthopedic surgery:

- The usual dose is **600 IU** per kilogram body weight, administered once a week.
- If your hemoglobin level is too high before the operation, EPREX treatment will be stopped.
- You may be given iron supplements before and during EPREX treatment to improve the effectiveness of the treatment.
- The preparation will be given by injection under the skin, once a week, for 3 weeks before the surgery and on the day of surgery.
- If there is a medical need to push up the surgery, the dosage will be **300 IU** per kilogram, once a day, for up to 10 days before the surgery, on the day of surgery and for 4 days after it.

Do not exceed the recommended dosage

At the beginning of treatment, EPREX will be injected by the medical staff. Later, your doctor may suggest self-injection under the skin that you or a caregiver/family member will perform.

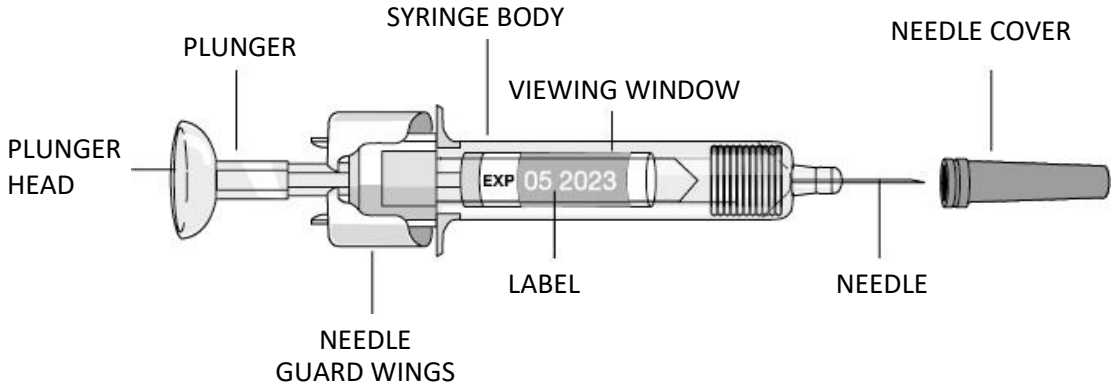
- Do not self-inject EPREX unless you have been trained to do so by the doctor

and/or nurse.

- Always use EPREX according to the doctor's and/or nurse's instructions.
- Only use EPREX that has been stored correctly. See section 5 "How should the medicine be stored?".
- Before using EPREX, leave the syringe out of the refrigerator until it reaches room temperature. This process takes about 15-30 minutes. Use the syringe immediately afterwards.
- Only take one dose from each EPREX syringe.
- When EPREX is injected under the skin, the amount injected should not exceed one milliliter in a single injection.
- The solution should be injected as is and must not be mixed with other liquids before the injection.
- Do not shake the EPREX syringe. Vigorous or prolonged shaking may damage the preparation. If the preparation has been shaken vigorously, do not use it.

Instructions for self-injection under the skin:

The EPREX syringe is fitted with a needle safety device to protect the injector from pricking/injury by the syringe needle after the injection. The device will automatically return the syringe and needle into the transparent plastic cylinder after injection of the contents of the syringe and release of the plunger.



- **Take the syringe out of the refrigerator.** The liquid in the syringe needs to reach room temperature. Do not remove the needle cover while waiting for the preparation to reach room temperature.
- **Check the syringe** to make sure it is the right dosage, that the expiry date has not passed, that the syringe is not damaged and that the liquid in the syringe is clear and has not been frozen.
- Remove the peelable portion of the label from the syringe. If you cannot see the numbered graduations through the viewing window, hold the body of the syringe and gently turn the syringe by the needle cover to line up the numbered graduations with the viewing window.

- **Choose the injection site.** An appropriate injection site is at the top of the thigh or the abdomen (not near the navel). Vary the injection site for each injection.
- **Wash your hands. Use an antiseptic pad to disinfect the injection site.**
- **Hold the syringe body, with the covered needle facing upward.**
- **Do not hold the plunger head, the plunger, the needle guard wings or the needle cover.**
- **Do not pull the plunger at any stage.**
- **Do not remove the needle cover, unless you are ready to inject EPREX to yourself.**
- **Take the needle cover off** by holding the syringe body and carefully pulling off the needle cover without twisting it. Do not touch the needle and do not shake the syringe.
- Remove the air bubble by holding the syringe with the needle pointing up and gently pressing the plunger until a drop of liquid comes out of the needle tip.
- If the doctor tells you to take only part of the dose in the syringe, push the plunger until the marking reaches the desired dosage and remove the excess fluid.
- **Do not touch the needle guard wings, to prevent premature covering of the needle with the guard device.**
- **Pinch a fold of skin** between your thumb and index finger. Do not squeeze firmly.
- **Insert the needle fully into the skin,** as instructed by the doctor or nurse.
- **Push the plunger with your thumb as much as you can to inject the entire amount of liquid.** Slowly and evenly press on the plunger, maintain your grip on the skin fold. The needle safety device will not activate unless the entire dose is injected. You may hear a click when the needle safety device has been activated.
- **When the plunger has been pushed as much as possible,** take out the needle and release the skin fold.
- **Slowly remove your thumb from the plunger** to allow the syringe to move up until the entire needle is covered by the needle safety device.
- **When the needle is pulled out of your skin, there may be a little bleeding at the injection site. This is normal. You can press an antiseptic pad** on the injection site for a few seconds after injecting.
- **Dispose of the used syringe** and the cover in a medical waste receptacle. See section 5 "How should the medicine be stored?".

If you accidentally injected a higher dose than required, tell the doctor or nurse immediately. Side effects from an overdose of EPREX are uncommon.

If you forget to inject the medicine at the required time, inject a dose as soon as you remember. Never inject two doses together!

If you forgot to inject and you remembered one day or less before the next injection, skip the forgotten injection and carry on with the original injection schedule.

If you have hepatitis C and you receive interferon and ribavirin, discuss it with

your doctor because a combination treatment of epoetin alfa with interferon and ribavirin showed a reduced effect and development of PRCA, which is a severe form of anemia, in rare cases. EPREX is not approved for use in patients with anemia associated with hepatitis C.

Adhere to the treatment regimen as recommended by the doctor.

Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the doctor.

Do not take medicines in the dark! Check the label and the dose each time you take medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the doctor, nurse or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of EPREX may cause side effects in some users. Do not be alarmed by reading the list of side effects. You may not suffer from any of them.

Tell the nurse or doctor immediately if you notice any of the side effects in this list.

Very common side effects – effects that occur in more than 1 in 10 users:

- Diarrhea.
- Nausea.
- Vomiting.
- Fever.
- Respiratory tract congestion, such as stuffy nose and sore throat, has been reported in patients with kidney disease not yet on dialysis.

Common side effects – effects that occur in 1-10 out of 100 users:

- Rise in blood pressure. Headaches, particularly sudden, stabbing migraine-like headaches, feeling confused or having fits may be signs of an increase in blood pressure. This requires urgent treatment. Raised blood pressure may require medicinal treatment (or adjustment of medicines you already take for high blood pressure).
- Blood clots (including deep vein thrombosis and embolism) that may require urgent treatment. You may have chest pain, breathlessness and painful swelling and redness, especially in the leg.
- Cough.
- Skin rash, which may result from an allergic reaction.
- Bone or muscle pain.
- Flu-like symptoms, such as headache, joint pain, feeling of weakness, chills, tiredness and dizziness. These effects may be more common at the start of treatment with the preparation. If you have these symptoms during injection into

the vein, a slower injection may help to avoid them in the future.
- Redness, burning and pain at the site of injection.
- Swelling of the ankles, feet and fingers.
- Pain in the leg or arm.

Uncommon side effects – effects that occur in 1-10 out of 1,000 users:
- High levels of blood potassium which can cause abnormal heart rhythm (this is a very common side effect in patients on dialysis).
- Fits.
- Nose or airway congestion.
- Allergic reaction.
- Hives.

Rare side effects – effects that occur in 1-10 out of 10,000 users:
- Symptoms of PRCA. PRCA causes sudden and severe anemia, characterized by:
  - unusual tiredness
  - feeling dizzy
  - breathlessness

  PRCA has been reported rarely in patients with chronic kidney failure after months and even years of EPREX use and also other preparations that stimulate red blood cell production.
- An increase in levels of thrombocytes (platelets), blood cells which are usually involved in the formation of blood clots, particularly at the beginning of treatment. Your doctor will check your platelet level.
- Severe allergic reaction that may lead to an itchy rash (hives), breathing difficulties, difficulty swallowing, swelling in the facial area, lips, mouth, tongue or throat.
- A problem with the blood that may cause pain, dark-colored urine or increased sensitivity of the skin to sunlight (porphyria).

If you are being treated by hemodialysis:
- Blood clots may form in the shunt. This is more likely if you have low blood pressure or if you have fistula-related complications.
- Blood clots may also form in the hemodialysis system. The doctor may decide to increase the heparin dosage during dialysis.

Severe skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in association with epoetin treatment. These rashes can manifest as reddish target-like spots or circular patches on the trunk, which usually also have blisters at their center, skin peeling, ulcers in the mouth, throat, nose, genital area, eyes. Fever and/or flu-like symptoms can precede these severe skin rashes.

If you develop a severe skin rash or any of these other skin symptoms, stop treatment with EPREX, contact your doctor or seek medical treatment immediately.

Tell the doctor or nurse immediately if you are aware of any of the side effects

mentioned in this section or if you notice any other effects during the course of treatment with EPREX.

If one of the side effects worsens, or if you suffer from a side effect not mentioned in the leaflet, consult with the attending doctor, nurse or pharmacist.

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects.

5. HOW SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine and any other medicine, should be kept in a safe place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) that appears on the package and the syringe. The expiry date refers to the last day of that month.
- Store EPREX in the refrigerator (2°C-8°C: this range is common in most household refrigerators). EPREX can be taken out of the refrigerator and stored at room temperature for up to 3 days. After the syringe has been taken out of the refrigerator and has reached room temperature, use it within 3 days or throw it out.
- Keep the preparation in its original package to prevent exposure to light.
- Do not freeze and do not shake the syringe. Do not use a syringe that has been vigorously shaken or frozen.
- Do not use EPREX if you notice that the syringe is broken, that the liquid is not clear or if you can see particles in the liquid.
- Do not dispose of the EPREX syringe down the toilet or in the household waste bin. Ask the pharmacist how to dispose of remnants of the medicine that are not being used. This will help protect the environment.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains:

Sodium chloride, sodium phosphate monobasic dihydrate, sodium phosphate dibasic dihydrate, glycine, polysorbate 80, water for injection.

What the medicine looks like and the contents of the package:

EPREX is provided as an injectable solution in a pre-filled syringe. The solution is clear, colorless and particle-free.

The pre-filled syringe has a needle protection device to protect from pricking.

There are 10 different dosages of EPREX.

The packages of the 2,000, 3,000, 4,000, 5,000, 6,000, 8,000 and 10,000 dosages contain 6 syringes.

The packages of the 20,000, 30,000 and 40,000 dosages contain one syringe.

Registration Holder and address: J-C Health Care Ltd., Kibbutz Shefayim 6099000, Israel.

Manufacturer:
CILAG AG, HOCHSTRASSE 201 CH-8205 SCHAFFHAUSEN, SWITZERLAND
Registration number of the medicine in the National Drug Registry of the Ministry of Health:

- EPREX 2,000 IU/0.5 ml: 116 78 29671
- EPREX 3,000 IU/0.3 ml: 116 79 29672
- EPREX 4,000 IU/0.4 ml: 116 80 29673
- EPREX 5,000 IU/0.5 ml: 123 41 30339
- EPREX 6,000 IU/0.6 ml: 123 42 30340
- EPREX 8,000 IU/0.8 ml: 123 44 30342
- EPREX 10,000 IU/ml: 116 81 29674
- EPREX 20,000 IU/0.5 ml: 138 30 31794
- EPREX 30,000 IU/0.75 ml: 138 31 31795
- EPREX 40,000 IU/ml: 126 52 30480

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