EPO STADA PREFILLED SYRINGE

Epoetin zeta (2 000 IU/0.6 ml, 4 000 IU/0.4ml, 10 000IU/1.0ml)

What is in this leaflet

This is a biosimilar medicinal product referenced to Epoetin alpha. It is not interchangeable or substitutes with the reference product.

What EPO STADA is used for

EPO STADA is used:

- in adults, children and adolescents on haemodialysis to treat symptomatic anaemia (low red blood cell counts) associated with chronic renal failure (kidney disease).
- in adult patients on peritoneal dialysis to treat symptomatic anaemia associated with chronic renal failure (kidney disease).
- in adult patients with renal insufficiency not yet on dialysis to treat severe anaemia associated with kidney disease accompanied by clinical symptoms.
- in adult patients with chemotherapy induced anaemia
- in adult surgery patients in an autologous predonation programme.

How EPO STADA works

EPO STADA contains a protein called epoetin zeta, that stimulates the bone marrow to produce more red blood cells which carry haemoglobin (a substance that transports oxygen). Epoetin zeta is a copy of the human protein erythropoietin and acts in the same way.

Before you use EPO STADA

- *When you must not use it*
  - If you are allergic (hypersensitive) to erythropoietins or any of the other ingredients of this medicine (listed in ingredient).
  - if you have developed Pure Red Cell Aplasia (PRCA; reduced or stopped production of red blood cells) following treatment with any erythropoietin
  - if you have high blood pressure, which is not properly controlled with blood pressure-lowering medicines
  - if you cannot be given medicines to thin blood for the prevention of blood clots
  - if you are donating your own blood before surgery, and:
    - you had a heart attack or stroke in the month before your treatment
    - you have unstable angina pectoris (new or increasing chest pain)
    - you are at risk of blood clots in the veins (deep venous thrombosis). For example, if you have had clots before.

- *Before you start to use it*

  Talk to your doctor before using EPO STADA if you know you are suffering, or have suffered, from any of the following:
  - epileptic seizures
  - liver disease
  - cancer
  - anaemia from other causes
  - heart disease (such as angina)
  - disorders of blood circulation resulting in pins and needles or cold hands or feet or muscle cramps in the legs
    - blood clots/blood clotting disorders
    - kidney disease.

- *Taking other medicine*

  Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines.

  In particular, if you are taking a medicine containing the active substance cyclosporine to suppress your immune system after a kidney transplant, your doctor may order special blood tests to measure cyclosporine levels while you are taking EPO STADA.

  Iron supplements and other blood stimulants may increase the effectiveness of EPO STADA. Your doctor will decide if it is right for you to take them.

How to use EPO STADA

EPO STADA therapy is usually started under medical supervision. The injections can then be given by a doctor, trained nurse or other health care professional.

In case EPO STADA is injected under the skin (subcutaneously) you can also inject the solution yourself once you have been shown how. Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

- *Changing from injecting into a vein to injecting under the skin (from intravenous into subcutaneous injection)*

  Once your condition is controlled you will receive regular doses of EPO STADA. Your doctor may decide that it is better for you to receive EPO STADA by injection under the skin (subcutaneous) rather than into a vein (intravenous).

  The dose should remain the same while the change is being made. Afterwards, your doctor may order blood tests to see if any adjustment in dose is required.

- *Injecting EPO STADA under the skin yourself*

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

- *How much to use*

  The dose you receive is based on your body weight in kilograms. Your doctor will conduct investigations, for example blood tests, to help decide if it is necessary for you to have EPO STADA. He/she will work out the correct dose of EPO STADA for you

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to use, how long the treatment should continue and by what route the medicine will be given. These decisions will be influenced by what is causing your anemia. You may be given iron supplements before and during EPO STADA treatment to make it more effective.

- <u>*When to use it*</u>

• *Use in kidney disease patients* EPO STADA should be administered either under the skin (subcutaneously) or as an injection either into a vein or a tube that goes into a vein.

• *Use in adult patients receiving haemodialysis*
Your doctor will maintain your hemoglobin concentration between 10 and 12 g/dl (6.2 - 7.5 mmol/l).
EPO STADA may be given during the dialysis session or after you have received a dialysis session.
The recommended starting dose of EPO STADA is 50 IU/kg (International Units per kilogram). This is given 3 times a week. If the solution is given into a vein, it should be injected over 1-5 minutes. Depending on how your anemia responds to treatment, the dose may be adjusted approximately every 4 weeks until your condition is controlled. The dose you receive should not normally exceed 200 IU/kg 3 times a week. Your doctor will order regular blood tests to ensure that your medicine is continuing to work properly. When your condition has been brought under control, you will receive regular doses of EPO STADA, 2 or 3 times a week. These doses may not be as high as those received initially.

• *Use in children and adolescents up to 18 years receiving haemodialysis*
In children the doctor will maintain the hemoglobin concentration between 9.5 and 11 g/dl EPO STADA should be given after the patient has received a dialysis session. The dose for children and adolescents is based on body weight in kilograms. The recommended starting dose is 50 IU/kg. This is given three times a week, injected into a vein (over 1-5 minutes). Depending on how the anemia responds, the dose may be adjusted approximately every 4 weeks until the condition is controlled. Your doctor will order regular blood tests to see that this is being achieved.

• *Use in adult patients receiving peritoneal dialysis*
Your doctor will maintain your hemoglobin concentration between 10 and 12 g/dl. The recommended starting dose is 50 IU/kg. This is given twice a week. Depending on how your anemia responds, the dose may be adjusted approximately every 4 weeks until your condition is controlled. The total weekly dose that you receive should not normally exceed 200 IU/kg.
Your doctor will order regular blood tests to ensure that your medicine is continuing to work properly.

• *Use in adult patients with kidney disease but not receiving dialysis*
The recommended starting dose is 50 IU/kg. This is given 3 times a week. The starting dose may be adjusted by your doctor until your condition is controlled. After your condition has been brought under control, you will receive regular doses of EPO STADA, 3 times a week. The dosage should not normally exceed 200 IU/kg, 3 times a week.
Your doctor will order regular blood tests to ensure that your medicine is continuing to work properly.

• *Use in patients with chemotherapy induced anaemia*
EPO STADA should be administered by the subcutaneous route to patients with anaemia (e.g. haemoglobin concentration ≤10 g/dl (6.2 mmol/l). Anaemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician s evaluation of the individual patient´s clinical course and condition is necessary.
Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed. Haemoglobin variability should be addressed through dose management. Patients should be monitored closely to ensure that the lowest approved dose of EPO STADA is used to provide adequate control of the symptoms of anaemia.

EPO STADA therapy should continue until one month after the end of chemotherapy.
The initial dose is 150 IU/kg given subcutaneously 3 times per week. Alternatively, EPO STADA can be administered at an initial dose of 450 IU/kg subcutaneously once weekly.
Once the therapeutic objective for an individual patient has been achieved, the dose should be reduced by 25 to 50% in order to maintain haemoglobin at that level. Appropriate dose titration should be considered.

• *Dose adjustment*
At a rate of rise in haemoglobin of > 2 g/dl (> 1.25 mmol/l) per month the EPO STADA dose should be reduced by about 25- 50%. If haemoglobin level exceeds 12 g/dl (7.5 mmol/l), discontinue therapy until it falls to 12 g/dl (7.5 mmol/l) or lower and then reinstitute Silapo therapy at a dose 25% below the previous dose.

• *Use in adult surgery patients in an autologous predonation programme.*
EPO STADA should be given by the intravenous route.
At the time of donating blood, EPO STADA should be administered after the completion of the blood donation procedure.
Mildly anaemic patients (haematocrit of 33-39%) requiring predeposit of ≥4 units of blood should be treated with EPO STADA at a dose of 600 IU/kg body weight 2 times weekly for 3 weeks prior to surgery.
All patients being treated with EPO STADA should receive adequate iron supplementation (e.g. 200 mg oral elemental iron daily) throughout the course of treatment. Iron supplementation should be started as soon as possible, even several weeks prior to initiating the autologous predeposit, in order to

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achieve high iron stores prior to starting EPO STADA therapy.

- *Information on administration*
  The pre-filled syringe is ready for use. Each syringe should be used for a single injection only. EPO STADA must not be shaken or mixed with any other liquid. If EPO STADA is injected under the skin the amount injected in any one place should not exceed 1 ml. Good injection sites are the top of the thigh and around the tummy (abdomen) but away from the navel. Vary the site from day to day.

- *If you forget to use it*
  Do not use a double dose to make up for a forgotten dose.

  Do not to stop the treatment without consultation of your doctor.

  If you have any further questions on the use of this medicine, ask your doctor.

- *If you use too much (overdose)*
  EPO STADA has a wide safety margin and side effects due to an overdose of using EPO STADA are unlikely. You should inform the doctor or nurse immediately if you think too much EPO STADA has been injected

While you are using EPO STADA

- *Things you must do*
  Always follow these instructions when using EPO STADA:
  1. Take one sealed syringe blister and leave it to stand for a few minutes until it reaches room temperature prior to using it. This usually takes between 15 and 30 minutes.
  2. Remove the syringe from the blister and check that the solution is clear, colourless and practically free from visible particles.
  3. Remove the protective cap from the injection needle and expel air from the syringe and injection needle by holding the syringe vertically and gently pressing the plunger upwards.
  4. Inject the solution as you have been shown by your doctor. You should check with your doctor or pharmacist if you are not sure.

- *Things you must not do*
  Do not use EPO STADA if:
  - the blister sealing is broken or the blister is damaged in any way
  - the liquid is colored or you can see particles floating in it
  - any liquid has leaked out of the pre-filled syringe or condensation is visible within the sealed blister
  - you know or think it may have been accidentally frozen

- *Things to be careful of*
  During treatment with EPO STADA:
  Your doctor will check that your haemoglobin does not exceed a certain level, as high haemoglobin concentrations could put you at risk of having a problem of the heart or the blood vessels and could increase risk of myocardial infarction, stroke and death.
  Your doctor should try to keep your hemoglobin levels between 10 and 12 g/dL. The haemoglobin values should not exceed a value of 12 g/dl.
  Your doctor will monitor your blood pressure regularly while you are using EPO STADA. If you experience headaches, particularly sudden, stabbing migraine-like headaches or start to feel confused or have fits, tell your doctor or nursing staff immediately. These may be the warning signs of a sudden rise in blood pressure, which requires urgent treatment.
  There may be a rise in the level of platelets (cells that help blood clotting) during treatment with this medicine. This should improve during the course of the treatment. It is recommended that the platelet count is regularly checked during the first 8 weeks of therapy.
  Remember to tell your doctor that you are receiving EPO STADA if you have to visit the hospital or family doctor for any treatment including a blood test, as EPO STADA may affect the results.

Take special care with other products that stimulate red blood cell production:
EPO STADA is one of a group of products that stimulate the production of red blood cells like the human protein erythropoietin does. Your healthcare professional will always record the exact product you are using.

Kidney disease patients
Pure Red Cell Aplasia (PRCA) has been reported very rarely after months to years of subcutaneous treatment with other products containing erythropoietins and may not be ruled out with EPO STADA. PRCA means the inability to produce enough red blood cells in the bone marrow. If this occurs it can result in severe anaemia, the symptoms of which are unusual tiredness, feeling dizzy or breathlessness. PRCA may be caused by the production to antibodies against the erythropoietin product and, in the following, to your own erythropoietin.
You should discuss this information with your doctor. If PRCA, a very rare condition, occurs, the EPO STADA therapy will be stopped and your doctor will determine the best course of action to treat the anaemia. Although this complication is very rare, you should be aware that if you develop it, you would need to have regular blood transfusions, possibly lifelong, to treat your anaemia and the EPO STADA therapy would have to be discontinued. Tell your doctor immediately if you suddenly feel very tired or dizzy or suffer from shortness of breath. Your doctor can decide whether EPO STADA is not working properly for you and will end the treatment, if necessary. Chronic renal failure patients on erythropoietin should have their haemoglobin levels measured on a regular basis until a stable level is achieved, and periodically thereafter to minimise the risk of an increase in blood pressure. If you are a patient with chronic kidney disease, your doctor will check that your haemoglobin

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does not exceed a certain level as high haemoglobin could put you at risk of having a problem of the heart or the blood vessels and could increase risk of death. Increases in blood potassium have happened in isolated cases. In chronic renal failure patients, correction for anaemia may lead to increased appetite, and potassium and protein intake. If you are receiving dialysis treatment when you begin treatment with EPO STADA, your dialysis regimen may need to be adjusted to maintain urea, creatinine and potassium levels in the desired range. Your doctor will decide this.

Serum electrolytes (substances in your blood) should be monitored in chronic renal failure patients. If an elevated (or rising) serum potassium level is detected, your doctor may consider to stop the treatment with EPO STADA until the level is back to normal.

An increase in the dose of a particular blood-thinning medicine (heparin) during haemodialysis is often needed during the course of therapy with EPO STADA to minimize the risk of blood clotting. Blockage of the dialysis system is possible if heparinisation is not optimum.

Cancer patients

Cancer patients are more likely to suffer from blood clots if receiving erythropoietin medicines, like EPO STADA. Therefore, you should discuss the benefits of EPO STADA with your doctor, particularly if you are obese or have a history of blood clots/blood clotting disorders.

Cancer patients on erythropoietin should have hemoglobin (the part of a red blood cell that carries oxygen) levels measured on a regular basis until a stable level is achieved, and periodically thereafter.

If you are a cancer patient, you should be aware that EPO STADA may act as a blood cell growth factor and in some circumstances may have a negative impact on your cancer. Depending on your individual situation a blood transfusion may be preferable. Please discuss this with your doctor.

Pregnancy and breast-feeding.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

If you are pregnant or breast-feeding, EPO STADA should be used only if the potential benefit outweighs the potential risk to the fetus.

Ask your doctor for advice before taking any medicine.

Driving and using machines

EPO STADA has no or negligible effect on the ability to drive and use machines.

EPO STADA contains phenylalanine

This medicine contains phenylalanine and may be harmful for people with phenylketonuria (genetic enzyme deficiency that increases excretion of a chemical (phenylketone) in urine and may cause nervous system disorders). This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium- free'.

Side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you experience headaches, particularly sudden, stabbing migraine-like headaches or feel confused or have fits, tell your doctor immediately. These may be the warning signs of a sudden rise in blood pressure which requires urgent treatment.

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

Very common side effects

These may affect more than 1 in 10 people using EPO STADA.

- Flu-like symptoms, headache, joint pain, feeling of weakness, tiredness and dizziness.

Common side effects

These may affect up to 1 in 10 people using EPO STADA.

- Increased blood pressure. Raised blood pressure may require treatment with drugs (or adjustment to any medicines you already take for high blood pressure). Your doctor may monitor your blood pressure regularly while you are using EPO STADA, particularly at the start of therapy.
- Chest pain, breathlessness, painful swelling in the leg which may be symptoms of blood clots (pulmonary embolism, deep vein thrombosis).
- Stroke (insufficient blood supply to the brain, which may lead to inability to move one or more limbs on one side of the body, inability to understand or formulate speech, or an inability to see one side of the visual field).
- Skin rash and swelling around the eyes (oedema), which may result from an allergic reaction.
- Blood clot in an artificial kidney.

Uncommon side effects

These may affect up to 1 in 100 people using EPO STADA.

- Cerebral hemorrhages.

Rare side effects

These may affect up to 1 in 1 000 people using EPO STADA.

- Hypersensitivity reactions.

Very rare side effects

These may affect up to 1 in 10 000 people using EPO STADA.

- Increased levels of small blood cells (called platelets), which are normally involved in the formation of a blood clot may occur. Your doctor will check on this.

Side effects with unknown frequency

The frequency of these side effects cannot be estimated from the available data.

- Swelling, mainly in the region of the eyelids and the lips (Quincke's edema) and shock- like allergic reactions with symptoms of tingling, reddening, itching, hot flush and accelerated pulse.
- Vascular and thrombotic events (blood clotting) in blood vessels

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such as disturbance of blood perfusion in the brain, retinal thrombosis, disturbed blood perfusion of the heart, heart attack, arterial thrombosis, dilatation of the wall of a blood vessel (aneurysm).
- Pure red cell aplasia (PRCA). PRCA has been reported in patients after months to years of subcutaneous (injection under the skin) erythropoietin treatment. PRCA means the inability to produce enough red blood cells in the bone (see section "Warnings and precautions").
- Itching (pruritus).

Other side effects:
Kidney patients
- raised blood pressure which may require treatment with medicinal products or adjustment of the dosage of medicinal products you already take for high blood pressure. Your doctor may monitor your blood pressure regularly while you are using EPO STADA, particularly at the start of therapy.
- Occlusion in the connection between artery and vein (shunt thrombosis) may occur especially if you have low blood pressure or if your arteriovenous fistula has complications. Your doctor may check your shunt and prescribe a medicinal product to prevent thrombosis.

Cancer patients
- blood clotting (thrombotic vascular events) increase of blood pressure. Therefore, your hemoglobin- levels and your blood pressure should be controlled.

If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet.

You may report any side effects or adverse drug reactions directly to the National Centre for Adverse Drug Reaction Monitoring by visiting the website npra.gov.my [Consumers→ Reporting Side Effects to Medicines (ConSERF) or Vaccines (AEFI)].

Storage and Disposal of EPO STADA
Storage
- Keep out of the reach and sight of children.
- Do not use this medicine after the expiry date which is stated on the label and the carton. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C). Do not freeze.
- Keep the pre-filled syringe in the outer carton in order to protect from light.
- The syringe can be removed from the refrigerator and left at room temperature for a single period of maximum 3 days (but not above 25°C).

Disposal
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist about how to throw away medicines you no longer use. These measures will help to protect the environment.

Product Description
What it looks like
- EPO STADA is presented as a clear and colorless solution for injection in a pre-filled syringe with a fixed injection needle.
- The pre-filled syringes contain between 0.4ml to 1.0ml solution, depending on the content of epoetin zeta.
- One pack contains 6 pre-filled syringes.

Ingredients
- Active ingredient:
  The active substance is epoetin zeta (produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cell line).

- Inactive ingredient:
  The other ingredients are disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, sodium chloride, calcium chloride dihydrate, polysorbate 20, glycine, leucine, isoleucine, threonine, glutamic acid, phenylalanine, water for injections, sodium hydroxide (pH adjuster), hydrochloric acid (pH adjuster).

- *MAL number(s):*
  EPO STADA 2000IU/0.6ml: MAL15105038ACZ

  EPO STADA 4000IU/0.4ml: MAL15105040ACZ

  EPO STADA 10000IU/1.0ml: MAL15105039ACZ

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