## 1. NAME OF THE MEDICINAL PRODUCT

EPO STADA 3333 IU/ML; solution for injection filled in syringe 3 sizes
EPO STADA 1 000 IU/0.3 ml solution for injection in pre-filled syringe
EPO STADA 2 000 IU/0.6 ml solution for injection in pre-filled syringe
EPO STADA 3 000 IU/0.9 ml solution for injection in pre-filled syringe

EPO STADA 10000 IU/ML: solution for injection filled in syringe 5 sizes
EPO STADA 4 000 IU/0.4 ml solution for injection in pre-filled syringe
EPO STADA 5 000 IU/0.5 ml solution for injection in pre-filled syringe
EPO STADA 6 000 IU/0.6 ml solution for injection in pre-filled syringe
EPO STADA 8 000 IU/0.8 ml solution for injection in pre-filled syringe
EPO STADA 10 000 IU/1 ml solution for injection in pre-filled syringe

EPO STADA 40000IU/ML; solution for injection filled in syringe 3 sizes
EPO STADA 20 000 IU/0.5 ml solution for injection in pre-filled syringe
EPO STADA 30 000 IU/0.75 ml solution for injection in pre-filled syringe
EPO STADA 40 000 IU/1 ml solution for injection in pre-filled syringe

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EPO STADA 1 000 IU/0.3 ml solution for injection in pre-filled syringe
1 pre-filled syringe with 0.3 ml solution for injection contains 1 000 international units (IU) epoetin zeta* (recombinant human erythropoietin). The solution contains 3 333 IU Epoetin zeta per ml.

*Excipient with known effect*
Each pre-filled syringe contains 0.15 mg phenylalanine.

EPO STADA 2 000 IU/0.6 ml solution for injection in pre-filled syringe
1 pre-filled syringe with 0.6 ml solution for injection contains 2 000 international units (IU) epoetin zeta* (recombinant human erythropoietin). The solution contains 3 333 IU Epoetin zeta per ml.

*Excipient with known effect*
Each pre-filled syringe contains 0.30 mg phenylalanine.

EPO STADA 3 000 IU/0.9 ml solution for injection in pre-filled syringe
1 pre-filled syringe with 0.9 ml solution for injection contains 3 000 international units (IU) epoetin zeta* (recombinant human erythropoietin). The solution contains 3 333 IU Epoetin zeta per ml.

*Excipient with known effect*
Each pre-filled syringe contains 0.45 mg phenylalanine.

EPO STADA 4 000 IU/0.4 ml solution for injection in pre-filled syringe
1 pre-filled syringe with 0.4 ml solution for injection contains 4 000 international units (IU) epoetin zeta* (recombinant human erythropoietin). The solution contains 10 000 IU Epoetin zeta per ml.

*Excipient with known effect*
Each pre-filled syringe contains 0.20 mg phenylalanine.

EPO STADA 5 000 IU/0.5 ml solution for injection in pre-filled syringe
1 pre-filled syringe with 0.5 ml solution for injection contains 5 000 international units (IU) epoetin zeta* (recombinant human erythropoietin). The solution contains 10 000 IU Epoetin zeta per ml.

*Excipient with known effect*
Each pre-filled syringe contains 0.25 mg phenylalanine.

EPO STADA 6 000 IU/0.6 ml solution for injection in pre-filled syringe
1 pre-filled syringe with 0.6 ml solution for injection contains 6 000 international units (IU) epoetin

zeta* (recombinant human erythropoietin). The solution contains 10 000 IU Epoetin zeta per ml.

*Excipient with known effect*
Each pre-filled syringe contains 0.30 mg phenylalanine.

EPO STADA 8 000 IU/0.8 ml solution for injection in pre-filled syringe
1 pre-filled syringe with 0.8 ml solution for injection contains 8 000 international units (IU) epoetin zeta* (recombinant human erythropoietin). The solution contains 10 000 IU Epoetin zeta per ml.

*Excipient with known effect*
Each pre-filled syringe contains 0.40 mg phenylalanine.

EPO STADA 10 000 IU/1 ml solution for injection in pre-filled syringe
1 pre-filled syringe with 1 ml solution for injection contains 10 000 international units (IU) epoetin zeta* (recombinant human erythropoietin). The solution contains 10 000 IU Epoetin zeta per ml.

*Excipient with known effect*
Each pre-filled syringe contains 0.50 mg phenylalanine.

EPO STADA 20 000 IU/0.5 ml solution for injection in pre-filled syringe
1 pre-filled syringe with 0.5 ml solution for injection contains 20 000 international units (IU) epoetin zeta* (recombinant human erythropoietin). The solution contains 40 000 IU Epoetin zeta per ml.

*Excipient with known effect*
Each pre-filled syringe contains 0.25 mg phenylalanine.

EPO STADA 30 000 IU/0.75 ml solution for injection in pre-filled syringe
1 pre-filled syringe with 0.75 ml solution for injection contains 30 000 international units (IU) epoetin zeta* (recombinant human erythropoietin). The solution contains 40 000 IU Epoetin zeta per ml.

*Excipient with known effect*
Each pre-filled syringe contains 0.38 mg phenylalanine.

EPO STADA 40 000 IU/1 ml solution for injection in pre-filled syringe
1 pre-filled syringe with 1 ml solution for injection contains 40 000 international units (IU) epoetin zeta* (recombinant human erythropoietin). The solution contains 40 000 IU Epoetin zeta per ml.

*Excipient with known effect*
Each pre-filled syringe contains 0.50 mg phenylalanine.

For the full list of excipients, see section 6.1.

*Produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cell line.

## 3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.
Clear, colourless solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- Treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult and paediatric patients:
  - Treatment of anaemia associated with chronic renal failure in adult and paediatric patients on haemodialysis and adult patients on peritoneal dialysis (see section 4.4).

- Treatment of severe anaemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing dialysis (see section 4.4).

– Treatment of anaemia and reduction of transfusion requirements in adult patients receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, and at risk of anaemia at the start of chemotherapy).
– EPO STADA can be used to increase the yield of autologous blood from patients in a predonation programme. Its use in this indication must be balanced against the reported risk of thromboembolic events. Treatment should only be given to patients with moderate anaemia (no iron deficiency), 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).
– EPO STADA is indicated for non-iron deficient adults prior to major elective orthopaedic surgery having a high perceived risk for transfusion complications to reduce exposure to allogeneic blood transfusions. Use should be restricted to patients with moderate anaemia (e.g. haemoglobin concentration range between 10 to 13 g/dl) who do not have an autologous predonation programme available and with expected moderate blood loss (900 to 1 800 ml).
– EPO STADA can be used to increase haemoglobin concentration in symptomatic anaemia (haemoglobin concentration of ≤10 g/dl) in adults with low- or intermediate-1-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin (<200 mU/ml).

## 4.2 Posology and method of administration

Treatment with EPO STADA has to be initiated under the supervision of physicians experienced in the management of patients with above indications.

Posology

– *Treatment of symptomatic anaemia in adult and paediatric chronic renal failure patients*

EPO STADA should be administered either subcutaneously or intravenously.

The haemoglobin concentration aimed for is between 10 and 12 g/dl (6.2-7.5 mmol/l), except in paediatric patients in whom the haemoglobin concentration should be between 9.5 and 11 g/dl (5.9-6.8 mmol/l). The upper limit of the target haemoglobin concentration should not be exceeded.

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.

EPO STADA should be administered either subcutaneously or intravenously in order to increase haemoglobin to not greater than 12 g/dl (7.5 mmol/l). 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, with consideration for the haemoglobin target range of 10 g/dl (6.2 mmol/l) to 12 g/dl (7.5 mmol/l).

A sustained haemoglobin level of greater than 12 g/dl should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceeding 12 g/dl (7.5 mmol/l) are observed are described below. A rise in haemoglobin of greater than 2 g/dl (1.25 mmol/l) over a four week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.

Patients should be monitored closely to ensure that the lowest approved effective dose of EPO STADA is used to provide adequate control of the symptoms of anaemia whilst maintaining a haemoglobin concentration below or at 12g/dl (7.5 mmol/l).

Caution should be exercised with escalation of EPO STADA doses in patients with chronic renal failure. In patients with a poor haemoglobin response to EPO STADA, alternative explanations for the poor response should be considered (see sections 4.4 and 5.1).

In patients with chronic renal failure and clinically evident ischaemic heart disease or congestive heart failure, maintenance haemoglobin concentration should not exceed the upper limit of the target haemoglobin concentration.

*Adult patients on haemodialysis*

EPO STADA should be administered either subcutaneously or

intravenously. The treatment is divided into two stages:

1. Correction phase: 50 IU/kg 3 times per week. When a dose adjustment is necessary, this should be done in steps of at least four weeks. At each step, the increase or reduction in dose should be of 25 IU/kg 3 times per week.
2. Maintenance phase: Dose adjustment in order to maintain haemoglobin (Hb) values at the desired level: Hb between 10 and 12 g/dl (6.2-7.5 mmol/l). The recommended total weekly dose is between 75 and 300 IU/kg.

The clinical data available suggest that those patients whose initial haemoglobin is very low (< 6 g/dl or < 3.75 mmol/l) may require higher maintenance doses than those whose initial anaemia is less severe (Hb > 8 g/dl or > 5 mmol/l).

*Paediatric patients on haemodialysis*

The treatment is divided into two stages:

1. Correction phase 50 IU/kg, 3 times per week by the intravenous route. When a dose adjustment is necessary, this should be done in steps of 25 IU/kg, 3 times per week at intervals of at least 4 weeks until the desired goal is achieved.
2. Maintenance phase: Dose adjustment in order to maintain haemoglobin (Hb) values at the desired level: Hb between 9.5 and 11 g/dl (5.9-6.8 mmol/l).

Generally, children and adolescents under 30 kg body weight require higher maintenance doses than adults and children over 30 kg. The following maintenance doses were observed in clinical trials after 6 months of treatment.

| | Dose (IU/kg given 3 times per week) | |
|---|---|---|
| Weight (kg) | Median | Usual maintenance dose |
| < 10 | 100 | 75-150 |
| 10-30 | 75 | 60-150 |
| > 30 | 33 | 30-100 |

The clinical data available suggest that those patients whose initial haemoglobin is very low (< 6.8 g/dl or < 4.25 mmol/l) may require higher maintenance doses than those whose initial haemoglobin is higher > 6.8 g/dl or> 4.25 mmol/l).

*Adult patients on peritoneal dialysis*

EPO STADA should be administered either subcutaneously or

intravenously. The treatment is divided into two stages:

1. Correction phase: Starting dose of 50 IU/kg 2 times per week.
2. Maintenance phase: Dose adjustment in order to maintain haemoglobin (Hb) values at the desired level: Hb between 10 and 12 g/dl (6.2-7.5 mmol/l). Maintenance dose between 25 and 50 IU/kg 2 times per week into 2 equal doses.

*Adult patients with renal insufficiency not yet undergoing dialysis*

EPO STADA should be administered either subcutaneously or

intravenously. The treatment is divided into two stages:

1. Correction phase: Starting dose of 50 IU/kg 3 times per week, followed if necessary by a dose increase with 25 IU/kg increments (3 times per week) until the desired goal is achieved (this should be done in steps of at least four weeks).
2. Maintenance phase: During the maintenance phase, EPO STADA 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 haemoglobin (Hb) 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 20 000 IU) once weekly or 480 IU/kg (up to a maximum of 40 000 IU) once every 2 weeks.

– *Treatment of 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 with consideration for the haemoglobin target range of 10 g/dl (6.2 mmol/l) to 12 g/dl (7.5 mmol/l). A sustained haemoglobin level of greater than 12 g/dl (7.5 mmol/l) should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceeding 12 g/dl (7.5 mmol/l) are observed are described below.

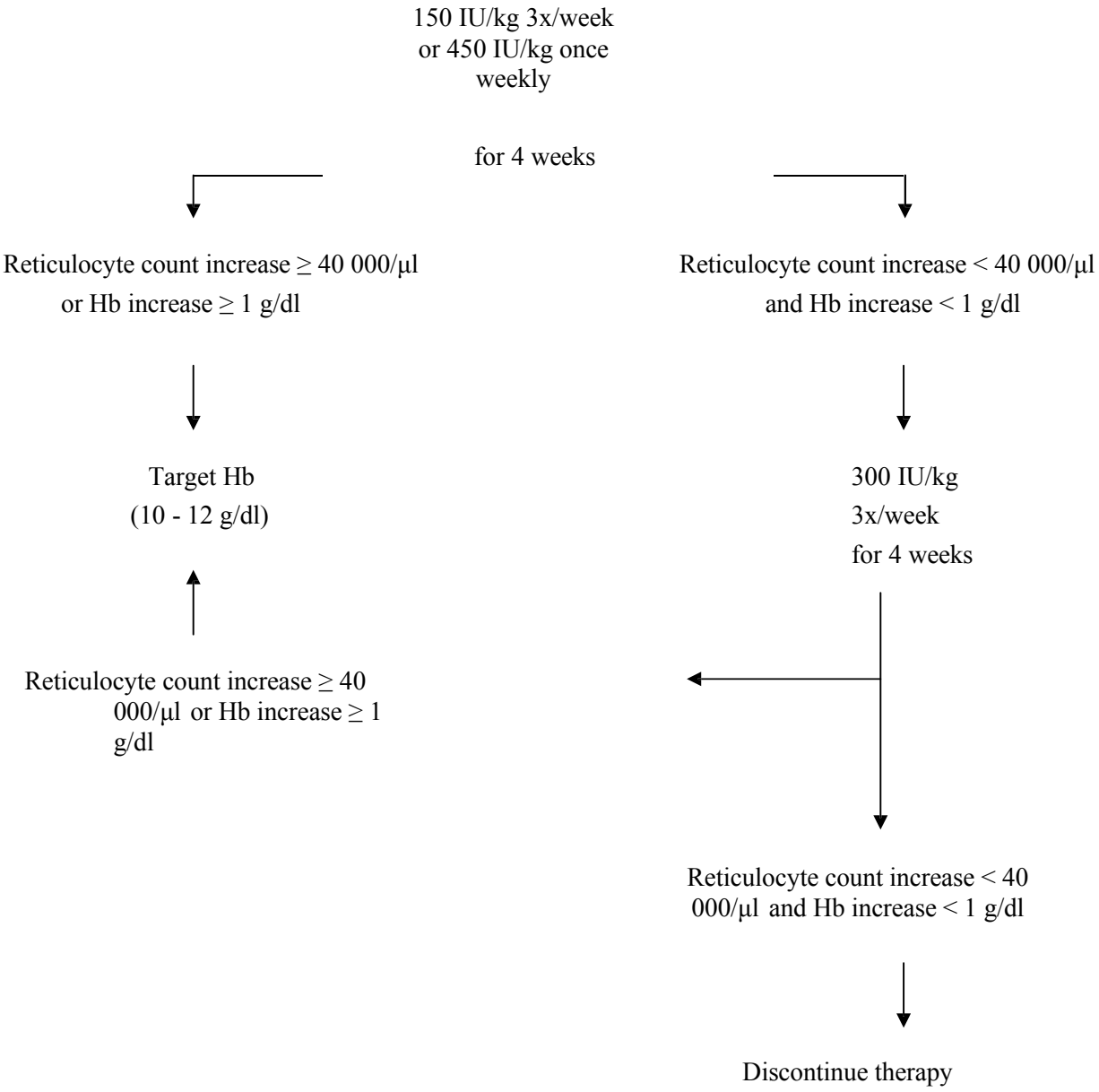
Patients should be monitored closely to ensure that the lowest approved dose of EPO STADA is used to provide adequate control of the symptoms of anaemia.

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.

If the haemoglobin has increased by at least 1 g/dl (0.62 mmol/l) or the reticulocyte count has increased ≥ 40 000 cells/µl above baseline after 4 weeks of treatment, the dose should remain at 150 IU/kg 3 times per week or 450 IU/kg once weekly. If the haemoglobin increase is < 1 g/dl (< 0.62 mmol/l) and the reticulocyte count has increased < 40 000 cells/µl above baseline, increase the dose to 300 IU/kg 3 times per week. If after an additional 4 weeks of therapy at 300 IU/kg 3 times per week, the haemoglobin has increased ≥ 1 g/dl (0.62 mmol/l) or the reticulocyte count has increased ≥ 40 000 cells/µl the dose should remain at 300 IU/kg 3 times per week. However, if the haemoglobin has increased < 1 g/dl (< 0.62 mmol/l) and the reticulocyte count has increased < 40 000 cells/µl above baseline, response is unlikely and treatment should be discontinued.

The recommended dosing regimen is described in the following diagram:




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 EPO STADA therapy at a dose 25% below the previous dose.

– *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 achieve high iron stores prior to starting EPO STADA therapy.

– *Treatment of adult patients scheduled for major elective orthopaedic surgery*

EPO STADA should be administered subcutaneously.

The recommended dose is 600 IU/kg administered subcutaneously weekly for three weeks (days -21, -14 and -7) prior to surgery and on the day of surgery.

In cases where there is a medical need to shorten the lead time before surgery to less than three weeks, 300 IU/kg should be administered subcutaneously daily for 10 consecutive days prior to surgery, on the day of surgery and for four days immediately thereafter.

If the haemoglobin level reaches 15 g/dl, or higher, during the preoperative period, administration of EPO STADA should be stopped and further dosages should not be administered.

The safety and efficacy of epoetin zeta in paediatrics have not been established. No data are available.

– *Treatment of adult patients with low- or intermediate-1-risk MDS*

EPO STADA should be administered subcutaneously.

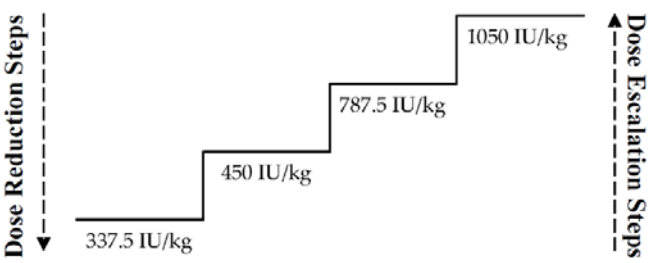
EPO STADA should be administered to patients with symptomatic anaemia (e.g. haemoglobin concentration
≤10 g/dl (6.2 mmol/l)).

The recommended starting dose of EPO STADA is 450 IU/kg (maximum total dose is 40 000 IU). This is given subcutaneously once every week, with not less than 5 days between doses.

Appropriate dose adjustments should be made to maintain haemoglobin concentrations within the target range of 10 g/dl to 12 g/dl (6.2 to 7.5 mmol/l). It is recommended that initial erythroid response be assessed 8 to 12 weeks following initiation of treatment. Dose increases and decreases should be done one dosing step at a time (see diagram below). A haemoglobin concentration of greater than 12 g/dl (7.5 mmol/l) should be avoided.

*Dose increase*
Dose should not be increased over the maximum of 1 050 IU/kg (total dose 80 000 IU) per week. If the patient loses response or haemoglobin concentration drops by ≥1 g/dl upon dose reduction the dose should be increased by one dosing step. A minimum of 4 weeks should elapse between dose increases.

*Dose hold and decrease*
EPO STADA should be withheld when the haemoglobin concentration exceeds 12 g/dl (7.5 mmol/l). Once the haemoglobin level is <11 g/dl the dose can be restarted on the same dosing step or one dosing step down based on physician judgement. Decreasing the dose by one dosing step should be considered if there is a rapid increase in haemoglobin (>2 g/dl over 4 weeks).



Anaemia symptoms and sequelae may vary with age, gender, and co-morbid medical conditions; a physician's evaluation of the individual patient's clinical course and condition is necessary.

Method of administration

*Intravenous injection*
The dose should be administered over at least 1-5 minutes, depending on the total dose. In haemodialysed patients, a bolus injection may be given during the dialysis session through a suitable venous port in the dialysis line. Alternatively, the injection can be given at the end of the dialysis session via the fistula needle tubing, followed by 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection to rinse the tubing and ensure satisfactory injection of the medicinal product into the circulation.

A slower injection is preferable in patients who react to the treatment with “flu-like” symptoms. EPO

STADA must not be administered by intravenous infusion.
EPO STADA must not be mixed with other medicinal products (see section 6.2).
*Subcutaneous injection*
A maximum volume of 1 ml at one injection site should generally not be exceeded. In case of larger volumes, more than one site should be chosen for the injection.

The injections are given in the limbs or the anterior abdominal wall.

For instructions on handling of the medicinal product before administration, see section 6.6.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients who develop Pure Red Cell Aplasia (PRCA) following treatment with any erythropoietin must not receive EPO STADA or any other erythropoietin (see section 4.4).
- Uncontrolled hypertension.
- In the indication "increasing the yield of autologous blood": myocardial infarction or stroke in the month preceding treatment, unstable angina pectoris, increased risk of deep venous thrombosis such as history of venous thromboembolic disease.
- The use of EPO STADA in patients scheduled for major elective orthopaedic surgery and not participating in an autologous blood predonation programme is contraindicated in patients with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including patients with recent myocardial infarction or cerebral vascular accident.
- Patients who for any reason cannot receive adequate antithrombotic prophylaxis.

## 4.4 Special warnings and precautions for use

*General*

Like in all patients receiving erythropoietin, blood pressure may rise during treatment with EPO STADA. Blood pressure should be closely monitored and adequately controlled in all epoetin treatment naïve as well as pre-treated patients before, at initiation of, and during treatment with EPO STADA. It may be necessary to add or increase anti-hypertensive treatment. If blood pressure cannot be well controlled, EPO STADA treatment should be discontinued.

EPO STADA should also be used with caution in the presence of epilepsy and chronic liver failure.

There may be a moderate dose-dependent rise in the platelet count within the normal range during treatment with erythropoietin. This regresses during the course of continued therapy. It is recommended that the platelet count is regularly monitored during the first 8 weeks of therapy.

All other causes of anaemia (iron deficiency, haemolysis, blood loss, vitamin $B_{12}$- or folate deficiencies) should be considered and treated prior to initiating and during therapy with EPO STADA. 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 erythropoietin, adequate iron stores should be assured:

- iron supplementation, e.g. 200-300 mg/day orally (100-200 mg/day for paediatric patients) is recommended for chronic renal failure patients whose serum ferritin levels are below 100 ng/ml
- oral iron substitution of 200-300 mg/day is recommended for all cancer patients whose transferrin saturation is below 20%.
- For patients scheduled for major elective orthopaedic surgery, iron supplementation (elemental iron 200 mg/day orally) should be administered throughout the course of epoetin zeta therapy. If possible, iron supplementation should be initiated prior to starting epoetin zeta therapy to achieve adequate iron stores.

All of these additive factors of anaemia should also be carefully considered when deciding to increase the dose of erythropoietin in cancer patients.

A paradoxical decrease in haemoglobin and development of severe anaemia associated with low reticulocyte counts should prompt to discontinue treatment with epoetin and perform anti-erythropoietin antibody testing. Cases have been reported in patients with hepatitis C treated with interferon and ribavirin, when epoetins are used concomitantly. Epoetins are not approved in the management of anaemia associated with hepatitis C.

In order to improve the traceability of erythropoiesis-stimulating agents (ESAs), the name of the prescribed ESA should be clearly recorded (or: stated) in the patient file.

Patients scheduled for major elective orthopaedic surgery

Good blood management practices should always be used in the perisurgical setting.

Patients scheduled for major elective orthopaedic surgery should receive adequate antithrombotic prophylaxis, as thrombotic and vascular events may occur in surgical patients, especially in those with underlying cardiovascular disease. In addition, special precaution should be taken in patients with predisposition for development of DVTs. Moreover, in patients with a baseline haemoglobin of > 13 g/dl, the possibility that epoetin zeta treatment may be associated with an increased risk of postoperative thrombotic/vascular events cannot be excluded. Therefore, epoetin zeta should not be used in patients with baseline haemoglobin > 13 g/dl.

*Chronic renal failure patients*

*Haemoglobin concentration*
In patients with chronic renal failure, maintenance haemoglobin concentration should not exceed the upper limit of the target haemoglobin concentration recommended in section 4.2. In clinical trials, an increased risk of death, serious cardiovascular events or cerebrovascular events including stroke were observed when ESAs were administered to target a haemoglobin of greater than 12 g/dl (7.5 mmol/l).

Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when haemoglobin concentration is increased beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.

Haemoglobin levels should be measured on a regular basis until a stable level is achieved and periodically thereafter. The rate of increase in haemoglobin should be approximately 1 g/dl (0.62 mmol/l) per month and should not exceed 2 g/dl (1.25 mmol/l) per month to minimise the risk of developing or worsening of hypertension.

Chronic renal failure patients treated with EPO STADA by the subcutaneous route should be monitored regularly for loss of efficacy, defined as absent or decreased response to EPO STADA treatment in patients

who previously responded to such therapy. This is characterised by a sustained decrease in haemoglobin despite an increase in EPO STADA dosage.

Some patients with more extended dosing intervals (greater than once weekly) of epoetin may not maintain adequate haemoglobin levels (see section 5.1) and may require an increase in epoetin dose. Haemoglobin levels should be monitored regularly.

Caution should be exercised with escalation of EPO STADA doses in patients with chronic renal failure, since high cumulative epoetin doses may be associated with an increased risk of mortality, serious cardiovascular and cerebrovascular events. In patients with a poor haemoglobin response to epoetins, alternative explanations for the poor response should be considered (see sections 4.2 and 5.1).

Non response to erythropoietin therapy should prompt a search for causative factors. These include: iron, folate, or Vitamin $B_{12}$ deficiency; aluminium intoxication; intercurrent infections; inflammatory or traumatic episodes; occult blood loss; haemolysis, and bone marrow fibrosis of any origin.

Cases of antibody-mediated PRCA have been very rarely reported in chronic renal failure patients with erythropoietin administered by the subcutaneous route. In patients developing sudden lack of efficacy, defined by a decrease in haemoglobin (1-2 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 $B_{12}$-deficiency, aluminium intoxication, infection or inflammation, blood loss, and haemolysis) should be investigated. If no cause is identified, a bone marrow examination should be considered for diagnosis of PRCA.

If PRCA is diagnosed, therapy with EPO STADA must be immediately discontinued and testing for erythropoietin antibodies should be considered. Patients should not be switched to another medicinal product as anti-erythropoietin antibodies cross-react with other erythropoietins. Other causes of PRCA should be excluded, and appropriate therapy initiated.

Monitoring of reticulocyte count on a regular basis is recommended to detect possible occurrence of lack of efficacy in chronic renal failure patients.

Hyperkalaemia has been observed in isolated cases. In chronic renal failure patients, correction for anaemia may lead to increased appetite, and potassium and protein intake. Dialysis prescriptions may have to be adjusted periodically to maintain urea, creatinine and potassium in the desired range. Serum electrolytes should be monitored in chronic renal failure patients. If an elevated (or rising) serum potassium level is detected then consideration should be given to ceasing erythropoietin administration until hyperkalaemia has been corrected.

An increase in heparin dose during haemodialysis is frequently required during the course of therapy with erythropoietin as a result of the increased packed cell volume. Occlusion of the dialysis system is possible if heparinisation is not optimum.

Based on information available to date, correction of anaemia with erythropoietin in adult patients with renal insufficiency not yet undergoing dialysis does not accelerate the rate of progression of renal insufficiency.

*Adult cancer patients with symptomatic anaemia receiving chemotherapy*

In cancer patients receiving chemotherapy, the 2-3 week delay between erythropoietin administration and the appearance of erythropoietin-induced red cells should be taken into account when assessing if EPO STADA therapy is appropriate (patient at risk of being transfused).

Haemoglobin levels should be closely monitored until a stable level is achieved and periodically thereafter. If the rate of increase in haemoglobin exceeds 2 g/dl (1.25 mmol/l) per month or the haemoglobin level exceeds 12 g/dl (7.5 mmol/l), the dose adjustment detailed in section 4.2 should be thoroughly performed to minimise the risk of thrombotic events (see section 4.2).

As an increased incidence of thrombotic vascular events (TVEs) has been observed in cancer patients receiving erythropoietic agents (see section 4.8), this risk should be carefully weighed against the benefit to be derived from treatment (with EPO STADA) particularly in cancer patients with an increased risk of thrombotic vascular events, such as obesity and patients with a prior history of TVEs (e.g. deep venous thrombosis or pulmonary embolism).

*Adult surgery patients in an autologous predonation programme*

All special warnings and precautions associated with autologous predonation programmes, especially routine volume replacement, should be respected.

*Tumour growth potential*

Epoetins are growth factors that primarily stimulate red blood cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells. As with all growth factors, there is a concern that epoetins could stimulate the growth of any type of malignancy. In several controlled studies, epoetins have not been shown to improve overall survival or decrease the risk of tumour progression in patients with anaemia associated with cancer.

Several controlled clinical studies in which epoetins were administered to patients with a variety of common tumours including squamous head and neck cancer, lung cancer, and breast cancer, have shown an unexplained excess mortality.

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

- shortened time to tumour progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a haemoglobin 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 target a haemoglobin of 12-14 g/dl (7.5 -8.7 mmol/l),
- increased risk of death when administered to target a haemoglobin 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, in some clinical situations blood transfusion should be the preferred treatment for the management of anaemia in patients with cancer. The decision to administer recombinant erythropoietins should be based on a benefit-risk assessment with the participation of the individual patient, which should take into account the specific clinical context. Factors that should be considered in this assessment should include the type of tumour and its stage; the degree of anaemia; life-expectancy; the environment in which the patient is being treated; and patient preference (see section 5.1).

*Severe cutaneous adverse reactions*

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with epoetin treatment. More severe cases have been observed with long-acting epoetins.

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, EPO STADA should be withdrawn immediately and an alternative treatment considered.
If the patient has developed a severe cutaneous skin reaction such as SJS or TEN due to the use of EPO STADA, treatment with EPO STADA must not be restarted in this patient at any time.

This medicinal product contains up to 0.5 mg phenylalanine in each dosage unit. Phenylalanine may be harmful for patients with phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

## 4.5 Interaction with other medicinal products and other forms of interaction

There is no evidence to indicate that treatment with erythropoietin alters the metabolism of other medicinal products.

However, since ciclosporin is bound by red blood cells there is potential for interactions with other medicinal products. If erythropoietin is given concomitantly with ciclosporin, blood levels of ciclosporin should be monitored and the dose of ciclosporin adjusted as the haematocrit rises.

No evidence exists that indicates an interaction between epoetin alfa and G-CSF or GM-CSF with regard to haematological differentiation or proliferation of tumour biopsy specimens in vitro.

## 4.6 Fertility, pregnancy and lactation

There are no adequate and well-controlled studies in pregnant women. Studies in animals have shown reproduction toxicity (see section 5.3). It is not known whether exogenous epoetin zeta is excreted in human milk. Consequently, erythropoietin should generally be used during pregnancy and lactation only if the potential benefit outweighs the potential risk to the foetus.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

Summary of the safety profile
Data from clinical studies with EPO STADA are in line with the safety profile of other authorised erythropoietins. Based on the results from clinical trials with other authorised erythropoietins approximately 8% of patients treated with erythropoietin are expected to experience adverse reactions. Adverse reactions during treatment with erythropoietin are observed predominantly in patients with chronic renal failure or underlying malignancies. These adverse reactions are most commonly headache and a dose dependent increase in blood pressure. Hypertensive crisis with encephalopathy-like symptoms can occur. Attention should be paid to sudden stabbing migraine-like headaches as a possible warning signal.

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.

Thrombotic/vascular events, such as myocardial ischaemia, myocardial infarction, cerebrovascular accidents (cerebral haemorrhage and cerebral infarction), transient ischaemic attacks, deep vein thrombosis, arterial thrombosis, pulmonary emboli, aneurysms, retinal thrombosis, and clotting of an artificial kidney have been reported in patients receiving erythropoietic agents.
Antibody-mediated erythroblastopenia (PRCA) has been reported after months to years of treatment with epoetin alfa. In most of these patients, antibodies to erythropoietins have been observed (see sections 4.3 and 4.4).

Tabulated list of adverse reactions
Of a total 3 417 subjects in 25 randomised, double-blinded, placebo or standard of care controlled studies, the overall safety profile of epoetin alfa was evaluated in 2 094 anaemic subjects. Included

were 228 epoetin alfa-treated CRF subjects in 4 chronic renal failure studies (2 studies in predialysis [N = 131 exposed CRF subjects] and 2 in dialysis [N = 97 exposed CRF subjects]); 1 404 exposed cancer subjects in 16 studies of anaemia due to chemotherapy; 147 exposed subjects in 2 studies for autologous blood donation; 213 exposed subjects in 1 study in the perisurgical period, and 102 exposed subjects in 2 MDS studies. Adverse drug reactions reported by ≥1% of subjects treated with epoetin alfa in these trials are shown in the table below.

Frequency estimate: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000), not known (frequency cannot be estimated from the available data).

| **MedDRA System Organ Classification (SOC)** | **Adverse Reaction (Preferred Term Level)** | **Frequency** |
|---|---|---|
| Blood and lymphatic system disorders | Pure red cell aplasia[3], Thrombocythemia | Rare |
| Metabolism and nutrition disorders | Hyperkalaemia[1] | Uncommon |
| Immune system disorders | Hypersensitivity[3] | Uncommon |
| | Anaphylactic reaction[3] | Rare |
| Nervous system disorders | Headache | Common |
| | Convulsion | Uncommon |
| Vascular disorders | Hypertension, Venous and arterial thromboses[2] | Common |
| | Hypertensive crisis[3] | Not known |
| Respiratory, thoracic and mediastinal disorders | Cough | Common |
| | Respiratory tract congestion | Uncommon |
| Gastrointestinal disorders | Diarrhoea, Nausea, Vomiting | Very common |
| Skin and subcutaneous tissue disorders | Rash | Common |
| | Urticaria[3] | Uncommon |
| | Angioneurotic oedema[3] | Not known |
| Musculoskeletal and connective tissue disorders | Arthralgia, Bone pain, Myalgia, Pain in extremity | Common |
| Congenital, familial and genetic disorders | Porphyria acute[3] | Rare |
| General disorders and administration site conditions | Pyrexia | Very common |
| | Chills, Influenza like illness, Injection site reaction, Oedema peripheral | Common |
| | Drug ineffective[3] | Not known |
| Investigations | Anti-erythropoeitin antibody positive | Rare |

[1] Common in dialysis

[2] Includes arterial and venous, fatal and non fatal events, such as deep venous thrombosis, pulmonary emboli, retinal thrombosis, arterial thrombosis (including myocardial infarction), cerebrovascular accidents (including cerebral infarction and cerebral haemorrhage) transient ischaemic attacks, and shunt thrombosis (including dialysis equipment) and thrombosis within arteriovenous shunt aneurisms

[3] Addressed in the subsection below and/or in section 4.4

Description of selected adverse reactions

*Adult and paediatric haemodialysis patients, adult peritoneal dialysis patients and adult patients with renal insufficiency not yet undergoing dialysis*

The most frequent adverse reaction during treatment with epoetin alfa is a dose-dependent increase in blood pressure or aggravation of existing hypertension. These increases in blood pressure can be treated with medicinal products. Moreover, monitoring of the blood pressure is recommended particularly at the start of therapy. The following reactions have also occurred in isolated patients with normal or low blood pressure: hypertensive crisis with encephalopathy-like symptoms (e.g. headaches and confused state) and generalised tonoclonal seizures, requiring the immediate attention of a physician and intensive medical care. Particular attention should be paid to sudden stabbing migraine like headaches as a possible warning signal.
Shunt thromboses may occur, especially in patients who have a tendency to hypotension or whose arteriovenous fistulae exhibit complications (e.g. stenoses, aneurysms, etc.). Early shunt revision and thrombosis prophylaxis by administration of acetylsalicylic acid, for example, is recommended in these patients.

*Adult cancer patients with symptomatic anaemia receiving chemotherapy*

Hypertension may occur in epoetin alfa treated patients. Consequently, haemoglobin and blood pressure should be closely monitored.
An increased incidence of thrombotic vascular events (see section 4.4 and section 4.8 - General) has been observed in patients receiving erythropoietic agents.

*Surgery patients*

Independent of erythropoietin treatment, thrombotic and vascular events may occur in surgical patients with underlying cardiovascular disease following repeated phlebotomy. Therefore, routine volume replacement should be performed in such patients.

In patients with a baseline haemoglobin of > 13 g/dl, the possibility that EPO STADA treatment may be associated with an increased risk of postoperative thrombotic/vascular events cannot be excluded.

*Adult patients with low- or intermediate-1-risk MDS*

In the randomised, double-blind, placebo-controlled, multicentre study 4 (4.7%) subjects experienced TVEs (sudden death, ischaemic stroke, embolism, and phlebitis). All TVEs occurred in the epoetin alfa group and in the first 24 weeks of the study. Three were confirmed TVE and in the remaining case (sudden death), the thromboembolic event was not confirmed. Two subjects had significant risk factors (atrial fibrillation, heart failure and thrombophlebitis).

*Severe cutaneous adverse reactions*

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with epoetin treatment (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

## 4.9 Overdose

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

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antianaemic preparations, erythropoietin
ATC code: B03XA01

EPO STADA is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Pharmacodynamic effects
Erythropoietin is a glycoprotein that stimulates, as a mitosis-stimulating factor and differentiating hormone, the formation of erythrocytes from precursors of the stem cell compartment.

The apparent molecular weight of erythropoietin is 32 000-40 000 Dalton. The protein moiety of the molecule contributes about 58% of total molecular weight and consists of 165 amino acids. The four carbohydrate chains are attached via three N-glycosidic bonds and one O-glycosidic bond to the protein. Epoetin zeta is identical in its amino acid sequence and similar in carbohydrate composition to endogenous human erythropoietin that has been isolated from the urine of anaemic patients.

The biological efficacy of erythropoietin has been demonstrated in various animal models *in vivo* (normal and anaemic rats, polycythaemic mice). After administration of erythropoietin, the number of erythrocytes, the Hb values and reticulocyte counts increase as well as the $^{59}$Fe-incorporation rate.

An increased $^{3}$H-thymidine incorporation in the erythroid nucleated spleen cells has been found *in vitro* (mouse spleen cell culture) after incubation with erythropoietin. It could be shown with the aid of cell cultures of human bone marrow cells that erythropoietin stimulates erythropoiesis specifically and does not affect leukopoiesis. Cytotoxic actions of erythropoietin on bone marrow cells could not be detected.

As with other haematopoietic growth factors, erythropoietin has shown *in vitro* stimulating properties on human endothelial cells.

*Adult patients with renal insufficiency not yet undergoing dialysis*

In 2 studies with extended interval dosing of erythropoietin (3 times per week, once weekly, once every 2 weeks and once every 4 weeks) some patients with longer dosing intervals did not maintain adequate haemoglobin levels and reached protocol-defined haemoglobin withdrawal criteria (0% in once weekly, 3.7% in once-every-2-weeks and 3.3% in the once-every-4-weeks groups).

*Treatment of adult patients scheduled for major elective orthopaedic surgery*
In patients scheduled for major elective orthopaedic surgery with a pretreatment haemoglobin of > 10 to ≤ 13 g/dl, epoetin alfa has been shown to decrease the risk of receiving allogeneic transfusions and hasten erythroid recovery (increased haemoglobin levels, haematocrit levels, and reticulocyte counts).

Clinical efficacy and safety
721 cancer patients receiving non-platinum chemotherapy were included in three placebo-controlled studies, 389 patients with haematological malignancies (221 multiple myeloma, 144 non-Hodgkin's lymphoma, and 24 other haematological malignancies) and 332 with solid tumours (172 breast,

64 gynaecological, 23 lung, 22 prostate, 21 gastrointestinal, and 30 other tumour types). In two large, open-label studies, 2 697 cancer patients receiving non-platinum chemotherapy were included, 1 895 with solid tumours (683 breast, 260 lung, 174 gynaecological, 300 gastrointestinal, and 478 other tumour types) and 802 with haematological malignancies.

In a prospective, randomised, double-blind, placebo-controlled trial conducted in 375 anaemic patients with various non-myeloid malignancies receiving non-platinum chemotherapy, there was a significant reduction of anaemia-related sequelae (e.g. fatigue, decreased energy, and activity reduction), as measured by the following instruments and scales: Functional Assessment of Cancer Therapy-Anaemia (FACT-An) general scale, FACT-An fatigue scale, and Cancer Linear Analogue Scale (CLAS). Two other smaller, randomised, placebo-controlled trials failed to show a significant improvement in quality of life parameters on the EORTC-QLQ-C30 scale or CLAS, respectively. Erythropoietin is a growth factor that primarily stimulates red cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells.

Survival and tumour progression have been examined in five large controlled studies involving a total of 2 833 patients, of which four were double-blind placebo-controlled studies and one was an open-label study. The studies either recruited patients who were being treated with chemotherapy (two studies) or used patient populations in which erythropoiesis stimulating agents are not indicated: anaemia in patients with cancer not receiving chemotherapy, and head and neck cancer patients receiving radiotherapy. The target haemoglobin concentration in two studies was > 13 g/dl; in the remaining three studies it was 12-14 g/dl. In the open-label study there was no difference in overall survival between patients treated with recombinant human erythropoietin and controls. In the four placebo-controlled studies the hazard ratios for overall survival ranged between 1.25 and 2.47 in favour of controls. These studies have shown a consistent unexplained statistically significant excess mortality in patients who have anaemia associated with various common cancers who received recombinant human erythropoietin compared to controls. Overall survival outcome in the trials could not be satisfactorily explained by differences in the incidence of thrombosis and related complications between those given recombinant human erythropoietin and those in the control group.

A systematic review has also been performed involving more than 9 000 cancer patients participating in 57 clinical trials. Meta-analysis of overall survival data produced a hazard ratio point estimate of 1.08 in favour of controls (95% CI: 0.99, 1.18; 42 trials and 8 167 patients). An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6 769 patients) was observed in patients treated with recombinant human erythropoietin. There is an increased risk for thromboembolic events in patients with cancer treated with recombinant human erythropoietin and a negative impact on overall survival cannot be excluded. The extent to which these outcomes might apply to the administration of recombinant human erythropoietin to patients with cancer, treated with chemotherapy to achieve haemoglobin concentrations less than 13 g/dl, is unclear because few patients with these characteristics were included in the data reviewed.

A patient-level data analysis has also been performed on more than 13 900 cancer patients (chemo-, radio-, chemoradio-, or no therapy) participating in 53 controlled clinical trials involving several epoetins. Meta-analysis of overall survival data produced a hazard ratio point estimate of 1.06 in favour of controls (95% CI: 1.00, 1.12; 53 trials and 13 933 patients) and for the cancer patients receiving chemotherapy, the overall survival hazard ratio was 1.04 (95% CI: 0.97, 1.11; 38 trials and 10 441 patients). Meta-analyses also indicate consistently a significantly increased relative risk of thromboembolic events in cancer patients receiving recombinant human erythropoietin (see section 4.4).

In a randomised, double-blind, placebo-controlled study of 4 038 CRF patients not on dialysis with type 2 diabetes and haemoglobin levels ≤ 11 g/dl, patients received either treatment with darbepoetin alfa to target haemoglobin levels of 13 g/dl or placebo (see section 4.4). The study did not meet either primary objective of demonstrating a reduction in risk for all-cause mortality, cardiovascular morbidity, or end stage renal disease (ESRD). Analysis of the individual components of the composite endpoints showed the following HR (95% CI): death 1.05 (0.92, 1.21), stroke 1.92 (1.38, 2.68),

congestive heart failure (CHF) 0.89 (0.74, 1.08), myocardial infarction (MI) 0.96 (0.75, 1.23), hospitalisation for myocardial ischaemia 0.84 (0.55, 1.27), ESRD 1.02 (0.87, 1.18).

Pooled post-hoc analyses of clinical studies of ESAs have been performed in CRF patients (on dialysis, not on dialysis, in diabetic and non-diabetic patients). A tendency towards increased risk estimates for all-cause mortality, cardiovascular and cerebrovascular events associated with higher cumulative ESA doses independent of the diabetes or dialysis status was observed (see sections 4.2 and 4.4).

**Major elective orthopaedic surgery**
The effect of epoetin alfa (300 IU/kg or 100 IU/kg) on the exposure to allogeneic blood transfusion has been evaluated in a placebo-controlled, double-blind clinical trial in non-iron deficient adult patients scheduled for major elective orthopaedic hip or knee surgery. Epoetin alfa was administered subcutaneously for 10 days prior to surgery, on the day of surgery, and for four days after surgery. Patients were stratified according to their baseline haemoglobin (≤ 10 g/dl, > 10 to ≤ 13 g/dl and > 13 g/dl).

Epoetin alfa 300 IU/kg significantly reduced the risk of allogeneic transfusion in patients with a pretreatment haemoglobin of > 10 to ≤ 13 g/dl. Sixteen percent of epoetin alfa 300 IU/kg, 23% of epoetin alfa 100 IU/kg and 45% of placebo-treated patients required transfusion.

An open-label, parallel-group trial in non-iron deficient adult subjects with a pretreatment haemoglobin of ≥ 10 to ≤ 13 g/dl who were scheduled for major orthopaedic hip or knee surgery compared epoetin alfa 300 IU/kg subcutaneously daily for 10 days prior to surgery, on the day of surgery and for four days after surgery to epoetin alfa 600 IU/kg subcutaneously once weekly for 3 weeks prior to surgery and on the day of surgery.

From pretreatment to presurgery, the mean increase in haemoglobin in the 600 IU/kg weekly group (1.44 g/dl) was twice than that observed in the 300 IU/kg daily group (0.73 g/dl). Mean haemoglobin levels were similar for the two treatment groups throughout the postsurgical period.

The erythropoietic response observed in both treatment groups resulted in similar transfusion rates (16% in the 600 IU/kg weekly group and 20% in the 300 IU/kg daily group).

**Treatment of adult patients with low- or intermediate-1-risk MDS**

A randomised, double-blind, placebo-controlled, multicentre study evaluated the efficacy and safety of epoetin alfa in adult anaemic subjects with low- or intermediate-1-risk MDS.

Subjects were stratified by serum erythropoetin (sEPO) level and prior transfusion status at screening. Key baseline characteristics for the <200 mU/ml stratum are shown in the table below.

| **Baseline Characteristics for Subjects with sEPO<200 mU/ml at Screening** | | |
|---|---|---|
| | Randomised | |
| | Epoetin alfa | Placebo |
| Total (N)[b] | 85[a] | 45 |
| Screening sEPO <200 mU/ml (N) | 71 | 39 |
| Haemoglobin (g/l) | | |
| N | 71 | 39 |
| Mean | 92.1 (8.57) | 92.1 (8.51) |
| Median | 94.0 | 96.0 |
| Range | (71, 109) | (69, 105) |
| 95% CI for Mean | (90.1, 94.1) | (89.3, 94.9) |
| Prior Transfusions | | |
| N | 71 | 39 |
| Yes | 31 (43.7%) | 17 (43.6%) |

| | | |
|---|---|---|
| ≤2 RBC Units | 16 (51.6%) | 9 (52.9%) |
| >2 and ≤4 RBC Units | 14 (45.2%) | 8 (47.1%) |
| >4 RBC Units | 1 (3.2%) | 0 |
| No | 40 (56.3%) | 22 (56.4%) |

[a] one subject did not have sEPO data
[b] in the ≥200 mU/ml stratum there were 13 subjects in the epoetin alfa group and 6 subjects in the placebo group

Erythroid response was defined according to International Working Group (IWG) 2006 criteria as a haemoglobin increase ≥1.5 g/dl from baseline or a reduction of RBC units transfused by an absolute number of at least 4 units every 8 weeks compared to the 8 weeks prior to baseline, and a response duration of at least 8 weeks.

Erythroid response during the first 24 weeks of the study was demonstrated by 27/85 (31.8%) of the subjects in the epoetin alfa group compared to 2/45 (4.4%) of the subjects in the placebo group ($p<0.001$). All of the responding subjects were in the stratum with sEPO <200 mU/ml during screening. In that stratum, 20/40 (50%) subjects without prior transfusions demonstrated erythroid response during the first 24 weeks, compared with 7/31 (22.6%) subjects with prior transfusions (two subjects with prior transfusion reached primary endpoint based on reduction of RBC units transfused by an absolute number of at least 4 units every 8 weeks compared to the 8 weeks prior to baseline).

Median time from baseline to first transfusion was statistically significantly longer in the epoetin alfa group compared to placebo (49 vs. 37 days; $p=0.046$). After 4 weeks of treatment the time to first transfusion was further increased in the epoetin alfa group (142 vs. 50 days, $p=0.007$). The percentage of subjects who were transfused in the epoetin alfa group decreased from 51.8% in the 8 weeks prior to baseline to 24.7% between weeks 16 and 24, compared to the placebo group which had an increase in transfusion rate from 48.9% to 54.1% over the same time periods.

## 5.2 Pharmacokinetic properties

*Intravenous route*
Measurement of erythropoietin following multiple dose intravenous administration revealed a half-life of approximately 4 hours in healthy volunteers and a somewhat more prolonged half-life of approximately 5 hours in renal failure patients. A half-life of approximately 6 hours has been reported in children.

*Subcutaneous route*
Following subcutaneous injection, serum levels of erythropoietin are much lower than the levels achieved following intravenous injection, the levels increase slowly and reach a peak between 12 and 18 hours postdose. The peak is always well below the peak achieved using the intravenous route (approximately 1/20th of the value).

There is no accumulation: the levels remain the same, whether they are determined 24 hours after the first injection or 24 hours after the last injection.

The half-life is difficult to evaluate for the subcutaneous route and is estimated to be about 24 hours. The bioavailability of subcutaneous injectable erythropoietin is much lower than that of the intravenous medicinal product and is approximately 20%.

## 5.3 Preclinical safety data

In some pre-clinical toxicological studies in dogs and rats, but not in monkeys, erythropoietin therapy was associated with subclinical bone marrow fibrosis (bone marrow fibrosis is a known complication of chronic renal failure in humans and may be related to secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis was not increased in a study of haemodialysis patients who were treated with erythropoietin for 3 years compared to a matched control group of dialysis patients who had not been treated with erythropoietin).

In animal studies, erythropoietin has been shown to decrease foetal body weight, delay ossification and increase foetal 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.

Erythropoietin did not show any changes in bacterial and mammalian cell culture mutagenicity tests and an *in vivo* micronucleus test in mice. Long-term carcinogenicity studies have not been carried out. There are conflicting reports in the literature regarding whether erythropoietin may play a major role as tumour proliferator. These reports are based on *in vitro* findings from human tumour samples, but are of uncertain significance in the clinical situation.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of Excipients

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)

### 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

30 months

### 6.4 Special precautions for storage

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.

For the purpose of ambulatory use, the patient may remove the product from the refrigerator and store it at room temperature (not above 25°C) for one single period of up to 3 days.

### 6.5 Nature and contents of container

EPO STADA 1 000 IU/0.3 ml solution for injection in pre-filled syringe
0.3 ml solution for injection in pre-filled syringe Type I glass with a fixed steel injection needle and a plunger stopper with PTFE coating.
Each pack contains 1 or 6 pre-filled syringes.

EPO STADA 2 000 IU/0.6 ml solution for injection in pre-filled syringe
0.6 ml solution for injection in pre-filled syringe Type I glass with a fixed steel injection needle and a plunger stopper with PTFE coating.
Each pack contains 1 or 6 pre-filled syringes.

EPO STADA 3 000 IU/0.9 ml solution for injection in pre-filled syringe
0.9 ml solution for injection in pre-filled syringe Type I glass with a fixed steel injection needle and a plunger stopper with PTFE coating.
Each pack contains 1 or 6 pre-filled syringes.

EPO STADA 4 000 IU/0.4 ml solution for injection in pre-filled syringe
1.4 ml solution for injection in pre-filled syringe Type I glass with a fixed steel injection needle and a plunger stopper with PTFE coating.
Each pack contains 1 or 6 pre-filled syringes.

EPO STADA 5 000 IU/0.5 ml solution for injection in pre-filled syringe
1.5 ml solution for injection in pre-filled syringe Type I glass with a fixed steel injection needle and a plunger stopper with PTFE coating.
Each pack contains 1 or 6 pre-filled syringes.

EPO STADA 6 000 IU/0.6 ml solution for injection in pre-filled syringe
1.6 ml solution for injection in pre-filled syringe Type I glass with a fixed steel injection needle and a plunger stopper with PTFE coating.
Each pack contains 1 or 6 pre-filled syringes.

EPO STADA 8 000 IU/0.8 ml solution for injection in pre-filled syringe
0.8 ml solution for injection in pre-filled syringe Type I glass with a fixed steel injection needle and a plunger stopper with PTFE coating.
Each pack contains 1 or 6 pre-filled syringes.

EPO STADA 10 000 IU/1 ml solution for injection in pre-filled syringe
1 ml solution for injection in pre-filled syringe Type I glass with a fixed steel injection needle and a plunger stopper with PTFE coating.
Each pack contains 1 or 6 pre-filled syringes.

EPO STADA 20 000 IU/0.5 ml solution for injection in pre-filled syringe
0.5 ml solution for injection in pre-filled syringe Type I glass with a fixed steel injection needle and a plunger stopper with PTFE coating.
Each pack contains 1 or 4 pre-filled syringes.

EPO STADA 30 000 IU/0.75 ml solution for injection in pre-filled syringe
0.75 ml solution for injection in pre-filled syringe Type I glass with a fixed steel injection needle and a plunger stopper with PTFE coating.
Each pack contains 1 or 4 pre-filled syringes.

EPO STADA 40 000 IU/1 ml solution for injection in pre-filled syringe
1 ml solution for injection in pre-filled syringe Type I glass with a fixed steel injection needle and a plunger stopper with PTFE coating.
Each pack contains 1 or 4 pre-filled syringes.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Handling instructions for EPO STADA:
1. After removing one syringe from the blister pack the solution should be checked to ensure that it is clear, colourless and practically free from visible particles.

2. The protective cap is removed from the injection needle and air is expelled from the syringe and needle by holding the syringe vertically and gently pressing the plunger upwards.
3. The syringe is now ready for use.

EPO STADA must not be used if
- The blister sealing is broken or the blister is damaged in any way.
- The liquid is coloured 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.
- It may have been accidentally frozen.

This medicinal product is for single use only.

Do not shake.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

STADA Arzneimittel AG
Stadastrasse 2-18
D-61118 Bad Vilbel
Germany

## 8. MARKETING AUTHORISATION NUMBER(S)

**EPO STADA 3333 IU/ML : TH Reg.no.**

EPO STADA 1 000 IU/0.3 ml solution for injection in pre-filled syringe TH Reg.no.

EPO STADA 2 000 IU/0.6 ml solution for injection in pre-filled syringe TH Reg.no.

EPO STADA 3 000 IU/0.9 ml solution for injection in pre-filled syringe TH Reg.no.

**EPO STADA 10000 IU/ML : TH Reg.no.**

EPO STADA 4 000 IU/0.4 ml solution for injection in pre-filled syringe TH Reg.no.

EPO STADA 5 000 IU/0.5 ml solution for injection in pre-filled syringe TH Reg.no.

EPO STADA 6 000 IU/0.6 ml solution for injection in pre-filled syringe TH Reg.no.

EPO STADA 8 000 IU/0.8 ml solution for injection in pre-filled syringe TH Reg.no.

EPO STADA 10 000 IU/1 ml solution for injection in pre-filled syringe TH Reg.no.

**EPO STADA 40000 IU/ML : TH Reg.no.**

EPO STADA 20 000 IU/0.5 ml solution for injection in pre-filled syringe TH Reg.no.

EPO STADA 30 000 IU/0.75 ml solution for injection in pre-filled syringe TH Reg.no.

EPO STADA 40 000 IU/1 ml solution for injection in pre-filled syringe TH Reg.no.

## 9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation:

## 10. DATE OF REVISION OF THE TEXT

16th October 2019