SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

WEPOX 5000 (Recombinant Human Erythropoietin injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Cartridge (3.0 ml) contains

Recombinant Human Erythropoietin 30000 IU

For full list of excipient see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

WEPOX is indicated for the treatment of symptomatic anaemia associated with chronic renal failure (CRF):

- In adults and paediatrics aged 1 to 18 years on haemodialysis and adult patients on peritoneal dialysis.
- In adults with renal insufficiency not yet undergoing dialysis for the treatment of severe anaemia of renal origin accompanied by clinical symptoms in patients.

WEPOX is indicated in adults receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy) for the treatment of anaemia and reduction of transfusion requirements.

WEPOX is indicated in adults in a predonation programme to increase the yield of autologous blood. Treatment should only be given to patients with moderate anaemia (haemoglobin concentration range between 10 to 13 g/dl [6.2 to 8.1 mmol/l], 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).

WEPOX 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).

4.2 Posology and method of administration

Posology

All other causes of anaemia (iron, folate or Vitamin B_{12} deficiency, aluminium intoxication, infection or inflammation, blood loss, haemolysis and bone marrow fibrosis of any origin) should be evaluated and treated prior to initiating therapy with epoetin, and when deciding to increase the dose. In order to ensure optimum response to epoetin, adequate iron stores should be assured and iron supplementation should be administered if necessary (see section 4.4).

Treatment of symptomatic anaemia in adult chronic renal failure patients

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.

The recommended desired haemoglobin concentration range is between 10 g/dl to 12 g/dl (6.2 to 7.5 mmol/l). WEPOX should be administered in order to increase haemoglobin to not greater than 12 g/dl (7.5 mmol/l). 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.

Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin concentration range may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin concentration 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. If the haemoglobin is rising by more than 2 g/dl (1.25 mmol/l) per month, or if the sustained haemoglobin exceeds 12 g/dl (7.5 mmol/l) reduce the WEPOX dose by 25%. If the haemoglobin exceeds 13 g/dl (8.1 mmol/l), discontinue therapy until it falls below 12 g/dl (7.5 mmol/l) and then reinstitute WEPOX therapy at a dose 25% below the previous dose.

Patients should be monitored closely to ensure that the lowest approved effective dose of WEPOX is used to provide adequate control of anaemia and of the symptoms of anaemia whilst maintaining a haemoglobin concentration below or at 12 g/dl (7.5 mmol/l). Caution should be exercised with escalation of ESA doses in patients with chronic renal failure. In patients with a poor haemoglobin response to ESA, alternative explanations for the poor response should be considered (see section 4.4 and 5.1).

Treatment with WEPOX is divided into two stages – correction and maintenance phase.

Adult haemodialysis patients

In patients on haemodialysis where intravenous access is readily available, administration by the intravenous route is preferable.

Correction phase:

The starting dose is 50 IU/kg, 3 times per week.

If necessary, increase or decrease the dose by 25 IU/kg (3 times per week) until the desired haemoglobin concentration range between 10 g/dl to 12 g/dl (6.2 to 7.5 mmol/l) is achieved (this should be done in steps of at least four weeks).

Maintenance phase:

The recommended total weekly dose is between 75 IU/kg and 300 IU/kg.

Appropriate adjustment of the dose should be made in order to maintain haemoglobin values within the desired concentration range between 10 g/dl to 12 g/dl (6.2 to 7.5 mmol/l).

Patients with very low initial haemoglobin (< 6 g/dl or < 3.75 mmol/l) may require higher maintenance doses than patients whose initial anaemia is less severe (> 8 g/dl or >
5 mmol/l).

Adult patients with renal insufficiency not yet undergoing dialysis
Where intravenous access is not readily available WEPOX may be administered subcutaneously. ***Correction phase***
Starting dose of 50 IU/kg, 3 times per week, followed if necessary by a dosage 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).
Maintenance phase
During the maintenance phase, WEPOX 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 values at the desired level: haemoglobin between 10 g/dl and 12 g/dl (6.2 to 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.

Adult peritoneal dialysis patients
Where intravenous access is not readily available WEPOX may be administered subcutaneously.
Correction phase The starting dose is 50 IU/kg, 2 times per week.
Maintenance phase
The recommended maintenance dose is between 25 IU/kg and 50 IU/kg, 2 times per week in 2 equal injections.
Appropriate adjustment of the dose should be made in order to maintain haemoglobin values at the desired level between 10 g/dl to 12 g/dl (6.2 to 7.5 mmol/l).

Treatment of adult patients with chemotherapy-induced anaemia
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.
WEPOX should be administered to patients with anaemia (e.g. haemoglobin concentration ≤ 10 g/dl (6.2 mmol/l)).
The initial dose is 150 IU/kg subcutaneously, 3 times per week.
Alternatively, WEPOX can be administered at an initial dose of 450 IU/kg subcutaneously once weekly.
Appropriate adjustment of the dose should be made in order to maintain haemoglobin concentrations within the desired concentration range between 10 g/dl to 12 g/dl (6.2 to 7.5 mmol/l).
Due to intra-patient variability, occasional individual haemoglobin concentrations for a patient above and below the desired haemoglobin concentration range may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the desired

haemoglobin concentration range between 10 g/dl (6.2 mmol/l) to 12 g/dl (7.5 mmol/l). A sustained haemoglobin concentration of greater than 12 g/dl (7.5 mmol/l) should be avoided; guidance for appropriate dose adjustment for when haemoglobin concentrations exceed 12 g/dl (7.5 mmol/l) are described below. If the haemoglobin concentration 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 concentration 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 concentration 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.
If the haemoglobin concentration 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.

Dose adjustment to maintain haemoglobin concentrations between 10 g/dl to 12 g/dl
If the haemoglobin concentration is increasing by more than 2 g/dl (1.25 mmol/l) per month, or if the haemoglobin concentration level exceeds 12 g/dl (7.5 mmol/l), reduce the EPREX dose by about 25 to 50%.
If the haemoglobin concentration level exceeds 13 g/dl (8.1 mmol/l), discontinue therapy until it falls below 12 g/dl (7.5 mmol/l) and then reinitiate EPREX therapy at a dose 25% below the previous dose.
Patients should be monitored closely to ensure that the lowest approved dose of erythropoiesis-stimulating agent (ESA) is used to provide adequate control of the symptoms of anaemia.
WEPOX therapy should continue until one month after the end of chemotherapy.

Treatment of adult surgery patients in an autologous predonation programme
Mildly anaemic patients (haematocrit of 33 to 39%) requiring predeposit of ≥ 4 units of blood should be treated with WEPOX 600 IU/kg intravenously, 2 times per week for 3 weeks prior to surgery. WEPOX should be administered after the completion of the blood donation procedure.

Treatment of adult patients scheduled for major elective orthopaedic surgery
The recommended dose is WEPOX 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, WEPOX 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 WEPOX should be stopped and further dosages should not be administered.

Paediatric population

Treatment of symptomatic anaemia in chronic renal failure patients on haemodialysis

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.

In paediatric patients the recommended haemoglobin concentration range is between 9.5 g/dl to 11 g/dl (5.9 to 6.8 mmol/l). WEPOX should be administered in order to increase haemoglobin to not greater than 11 g/dl (6.8 mmol/l). 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 dose of WEPOX is used to provide adequate control of anaemia and of the symptoms of anaemia. Treatment with WEPOX is divided into two stages – correction and maintenance phase. In paediatric patients on haemodialysis where intravenous access is readily available, administration by the intravenous route is preferable.

Correction phase

The starting dose is 50 IU/kg intravenously, 3 times per week.

If necessary, increase or decrease the dose by 25 IU/kg (3 times per week) until the desired haemoglobin concentration range of between 9.5 g/dl to 11 g/dl (5.9 to 6.8 mmol/l) is achieved (this should be done in steps of at least four weeks).

Maintenance phase

Appropriate adjustment of the dose should be made in order to maintain haemoglobin levels within the desired concentration range between 9.5 g/dl to 11 g/dl (5.9 to 6.8
mmol/l).

Generally, children under 30 kg require higher maintenance doses than children over 30 kg and adults.

Paediatric patients with very low initial haemoglobin (< 6.8 g/dl or < 4.25 mmol/l) may require higher maintenance doses than patients whose initial haemoglobin is higher (> 6.8 g/dl or > 4.25 mmol/l).

Anaemia in chronic renal failure patients before initiation of dialysis or on peritoneal dialysis

The safety and efficacy of epoetin in chronic renal failure patients with anaemia before initiation of dialysis or on peritoneal dialysis have not been established.

Treatment of paediatric patients with chemotherapy-induced anaemia

The safety and efficacy of epoetin in paediatric patients receiving chemotherapy have not been established.

Treatment of paediatric surgery patients in an autologous predonation programme

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

Treatment of paediatric patients scheduled for major elective orthopaedic surgery

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

Method of administration

Precautions to be taken before handling or administering the medicinal product
Before use, leave the WEPOX syringe to stand until it reaches room temperature. This usually takes between 15 and 30 minutes.

Treatment of symptomatic anaemia in adult chronic renal failure patients

In patients with chronic renal failure where intravenous access is routinely available (haemodialysis patients) administration of WEPOX by the intravenous route is preferable.
Where intravenous access is not readily available (patients not yet undergoing dialysis and peritoneal dialysis patients) WEPOX may be administered as a subcutaneous injection.

Treatment of adult patients with chemotherapy-induced anaemia WEPOX should be administered as a subcutaneous injection.

Treatment of adult surgery patients in an autologous predonation programme WEPOX should be administered by the intravenous route.

Treatment of adult patients scheduled for major elective orthopaedic surgery WEPOX should be administered as a subcutaneous injection.

Treatment of symptomatic anaemia in paediatric chronic renal failure patients on haemodialysis

In paediatric patients with chronic renal failure where intravenous access is routinely available (haemodialysis patients) administration of WEPOX by the intravenous route is preferable.

Intravenous administration

Administer over at least one to five 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 isotonic saline to rinse the tubing and ensure satisfactory injection of the product into the circulation (see Posology, *Adult haemodialysis patients*).
A slower administration is preferable in patients who react to the treatment with "flulike" symptoms (see section 4.8).

Do not administer WEPOX by intravenous infusion or in conjunction with other drug solutions.

Subcutaneous administration

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 should be given in the limbs or the anterior abdominal wall.
In those situations in which the physician determines that a patient or caregiver can safely and effectively administer WEPOX subcutaneously themselves, instruction as to the proper dosage and administration should be provided.
As with any other injectable product, check that there are no particles in the solution or change in colour.

4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients.
Patients who develop pure red cell aplasia (PRCA) following treatment with any erythropoietin should not receive WEPOX or any other erythropoietin (see section 4.4 - Pure Red Cell Aplasia).
Uncontrolled hypertension.
All contraindications associated with autologous blood predonation programmes should be respected in patients being supplemented with WEPOX.
The use of WEPOX 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.
Surgery patients who for any reason cannot receive adequate antithrombotic prophylaxis.

4.4 Special warnings and precautions for use

General

In all patients receiving epoetin, blood pressure should be closely monitored and controlled as necessary. Epoetin should be used with caution in the presence of untreated, inadequately treated or poorly controllable hypertension. It may be necessary to add or increase anti-hypertensive treatment. If blood pressure cannot be controlled, epoetin treatment should be discontinued.

Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have occurred also during epoetin treatment in patients with previously normal or low blood pressure. Particular attention should be paid to sudden stabbing migraine-like headaches as a possible warning signal.

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

Epoetin should be used with caution in patients with chronic liver failure. The safety of epoetin has not been established in patients with hepatic dysfunction.

An increased incidence of thrombotic vascular events (TVEs) has been observed in patients receiving ESAs (see section 4.8). These include venous and arterial thromboses and embolism (including some with fatal outcomes), such as deep venous thrombosis, pulmonary emboli, retinal thrombosis, and myocardial infarction. Additionally, cerebrovascular accidents (including cerebral infarction, cerebral haemorrhage and transient ischaemic attacks) have been reported.

The reported risk of these TVEs should be carefully weighed against the benefits to be derived from treatment with epoetin particularly in patients with pre-existing risk factors for TVE, including obesity and prior history of TVEs (e.g., deep venous thrombosis, pulmonary embolism, and cerebral vascular accident).

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

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

All other causes of anaemia (iron, folate or Vitamin B_{12} deficiency, aluminium intoxication, infection or inflammation, blood loss, haemolysis and bone marrow fibrosis of any origin) should be evaluated and treated prior to initiating therapy with epoetin, and when deciding to increase the dose. In most cases, the ferritin values in the serum fall simultaneously with the rise in packed cell volume. In order to ensure optimum response to epoetin, adequate iron stores should be assured and iron supplementation should be administered if necessary (see section 4.2):

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

Very rarely, development of or exacerbation of porphyria has been observed in epoetintreated patients. Epoetin should be used with caution in patients with porphyria.

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

Patients should only be switched from one ESA to another under appropriate supervision. **Pure Red Cell Aplasia**

Antibody-mediated pure red cell aplasia (PRCA) has been reported after months to years of subcutaneous epoetin treatment mainly in chronic renal failure patients. Cases have also been reported in patients with hepatitis C treated with interferon and ribavirin, when ESAs are used concomitantly. Epoetin is not approved in the management of anaemia associated with hepatitis C.

In patients developing sudden lack of efficacy defined by a decrease in haemoglobin (1 to 2 g/dl per month) with increased need for transfusions, a reticulocyte count should be obtained and typical causes of non-response (e.g. iron, folate or Vitamin B_{12} deficiency, aluminium intoxication, infection or inflammation, blood loss, haemolysis and bone marrow fibrosis of any origin) should be investigated.

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. A bone marrow examination should also be considered for diagnosis of PRCA.

No other ESA therapy should be commenced because of the risk of cross-reaction.

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

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

In chronic renal failure patients the rate of increase in 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 risks of an increase in hypertension.

In patients with chronic renal failure, maintenance haemoglobin concentration should not exceed the upper limit of the haemoglobin concentration range as recommended in section 4.2. In clinical trials, an increased risk of death and serious cardiovascular events was observed when ESAs were administered to achieve a haemoglobin concentration level 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.

Caution should be exercised with escalation of WEPOX 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.

Chronic renal failure patients treated with epoetin by the subcutaneous route should be monitored regularly for loss of efficacy, defined as absent or decreased response to epoetin treatment in patients who previously responded to such therapy. This is characterised by a sustained decrease in haemoglobin despite an increase in epoetin dosage.

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

Shunt thromboses have occurred in haemodialysis patients, especially in those 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.

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

An increase in heparin dose during haemodialysis is frequently required during the course of therapy with epoetin 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 epoetin in adult patients with renal insufficiency not yet undergoing dialysis does not accelerate the rate of progression of renal insufficiency.

Treatment of patients with chemotherapy-induced anaemia

Cancer patients being treated with epoetin should have haemoglobin levels measured on a regular basis until a stable level is achieved, and periodically thereafter.

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 tumours.

The role of ESAs on tumour progression or reduced progression-free survival cannot be excluded. In controlled clinical studies, use of ESAs have been associated with decreased locoregional tumour control or decreased overall survival.

Therefore, 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 erythropoietin treatment 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.

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

Surgery patients in autologous predonation programmes

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

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 baseline haemoglobin of > 13 g/dl, the possibility that epoetin treatment may be associated with an increased risk of postoperative thrombotic/vascular events cannot be excluded. Therefore, epoetin should not be used in patients with baseline haemoglobin > 13 g/dl.

4.5 Interactions with other medicaments and other forms of Interaction

No evidence exists that indicates that treatment with epoetin alters the metabolism of other drugs.

Drugs that decrease erythropoiesis may decrease the response to epoetin.

Since cyclosporin is bound by RBCs there is potential for a drug interaction. If epoetin is given concomitantly with cyclosporin, blood levels of cyclosporin should be monitored and the dose of cyclosporin adjusted as the haematocrit rises.

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

In female adult patients with metastatic breast cancer, subcutaneous co-administration of 40,000 IU/ml epoetin with trastuzumab 6 mg/kg had no effect on the pharmacokinetics of trastuzumab.

4.6 Pregnancy and lactation

WEPOX should be used during pregnancy, only if the potential benefit justifies the potential risk to the fetus. The use of epoetin alfa is not recommended in pregnant surgical patients participating in an autologous blood predonation. It is not known whether WEPOX is excreted into human milk and therefore it should

be used with caution in nursing women. The use of epoetin alfa is not recommended in lactating surgical patients participating in an autologous blood predonation programme.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed..

4.8 Undesirable effects

Summary of Safety Profile

The most frequent adverse drug reaction during treatment with epoetin alfa is a dosedependent increase in blood pressure or aggravation of existing hypertension. Monitoring of the blood pressure should be performed, particularly at the start of therapy (see section 4.4).

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

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

An increased incidence of thrombotic vascular events (TVEs) has been observed in patients receiving ESAs (see section 4.4).

List of Adverse Reactions

Blood and lymphatic system disorders: Erythropoietin antibody-mediated pure red cell aplasia, Thrombocythaemia

Metabolism and nutrition disorders: Hyperkalaemia

Immune system disorders: Anaphylactic reaction, Hypersensitivity

Nervous system disorders: Headache, Convulsions

Vascular disorders: Venous and arterial thrombosis*, Hypertension, Hypertensive crisis

Respiratory, thoracic and mediastinal disorders: Cough, Respiratory tract congestion

Gastrointestinal disorders: Diarrhoea, Nausea, Vomiting

Skin and subcutaneous tissue disorders: Rash, Angioneurotic oedema, Urticaria

Musculoskeletal and connective tissue disorders: Arthralgia, Bone pain, Myalgia, Pain in extremity

Congenital and familial/genetic disorders: Porphyria

General disorders and administration site conditions: Pyrexia, Chills, Influenza-like illness, Injection site reaction, Oedema peripheral, Drug ineffectiveness

* 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

Description of selected adverse reactions
Hypersensitivity reactions, including cases of rash (including urticaria), anaphylactic reactions, and angioneurotic oedema have been reported.
Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have occurred also during epoetin treatment in patients with previously normal or low blood pressure. Particular attention should be paid to sudden stabbing migraine-like headaches as a possible warning signal (see section 4.4).
Antibody-mediated pure red cell aplasia has been very rarely reported in cases after months to years of treatment with epoetin (see section 4.4).

Paediatric population with chronic renal failure on haemodialysis
The exposure of paediatric patients with chronic renal failure on haemodialysis is limited. No paediatric-specific adverse reactions not mentioned previously, or any that were not consistent with the underlying disease have been reported in this population.

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 Regulatory Authority.

4.9 Overdose
WEPOX has a very wide safety margin. In cases of overdosage, the pharmacological effects of the hormone are pronounced. When extremely high haemoglobin levels occur, phlebotomy may provide the solution. Supportive care is provided depending on the symptoms of overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: anti-anaemic, ATC code: B03XA01.
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 to 40,000 dalton. The protein fraction of the molecule contributes about 58% 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. Epoetinum obtained by gene technology is glycosylated and is identical in its amino acid and 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.

5.2 Pharmacokinetic properties

SC 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 half-life for the subcutaneous route is estimated to be about 24 hours.
The bioavailability of subcutaneous injectable erythropoietin is approximately 25%. IV route: The volume of distribution is similar to the plasma volume. When given by the intravenous route, the half -life is 5-6 hours, independent of the disease state.

5.3 Preclinical safety data

Mutagenecity, carcinogenecity and Impairment of fertility: Erythropoietin does not induce bacterial gene mutation (Ames test), chromosomal aberrations in mammalian cells, micro nuclei in mice, or gene mutation at the HGPRT locus. Carcinogenecity studies were not carried out. In rats and rabbits, when doses as large as 500 IU/Kg/day are given intravenously, there is no evidence of teratogenecity. Erythropoietin when given intravenously causes a slight but not statistically significant decrease in fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1. Human Serum Albumin
2. Sodium dihydrogen phosphate dihydrate
3. Disodium phosphate dihydrate
4. Sodium chloride
5. Water for injection

6.2 Incompatibilities

Not to be diluted or transferred to another container. Not to be administered along with other drug solutions.

6.3 Shelf Life

24 months from the date of manufacturing.

6.4 Special precautions for storage

Store between 2°C to 8°C, do not shake or freeze and do not expose to light.

6.5 Nature and contents of container

Clear, colourless solution, 0.4 ml filled in 1 ml long syringe, labeled, blister packed.

6.6 Instruction for use/handling

The product should not be used, and discarded

- if the seal is broken,

- if the liquid is coloured or you can see particles floating in it, • if you know, or think that it may have been accidentally frozen, or
- if there has been a refrigerator failure.

The product is for single use only. Only take one dose of WEPOX from each syringe removing unwanted solution before injection.

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

7. MARKETING AUTHORISATION HOLDER

Wockhardt Limited

8. MARKETING AUTHORISATION NUMBER

H2022/CTD9205/15287

9. DATE OF FIRST AUTHORISATION

Date of first authorization: March 11, 2004

10. DATE OF REVISION OF THE TEXT

25 October 2017