epoetin zeta

Retacrit 2 000 IU/0.6 ml solution for injection in pre-filled syringe
Retacrit 4 000 IU/0.4 ml solution for injection in pre-filled syringe
Retacrit 10 000 IU/1 ml solution for injection in pre-filled syringe
Retacrit 40 000 IU/1 ml solution for injection in pre-filled syringe

Reference market : UK (CP)

Markets using same as LPD:Kuwait&UAE

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Retacrit 2 000 IU/0.6 ml solution for injection in pre-filled syringe
Retacrit 4 000 IU/0.4 ml solution for injection in pre-filled syringe
Retacrit 10 000 IU/1 ml solution for injection in pre-filled syringe
Retacrit 40 000 IU/1 ml solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Retacrit 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.

Retacrit 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.

Retacrit 10 000 IU/1 ml solution for injection in pre-filled syringe
1 pre-filled syringe with 1.0 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.

Retacrit 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.

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

For the full list of excipients, see section 6.1.

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 transfusion as assessed by the patient's general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy).
- Retacrit 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).
- Retacrit can be used to reduce exposure to allogeneic blood transfusions in adult non-iron deficient patients prior to major elective orthopaedic surgery, having a high perceived risk for transfusion complications. Use should be restricted to patients with moderate anaemia (e.g. Hb 10-13 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

Treatment with Retacrit 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

Retacrit 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 sequaelea 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. Retacrit 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 Retacrit 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 Retacrit doses in patients with chronic renal failure. In patients with a poor haemoglobin response to Retacrit, 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 ischemic heart disease or congestive heart failure, maintenance haemoglobin concentration should not exceed the upper limit of the target haemoglobin concentration.

Adult patients on haemodialysis

Retacrit 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

Retacrit 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

Retacrit 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, Retacrit 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

Retacrit 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.

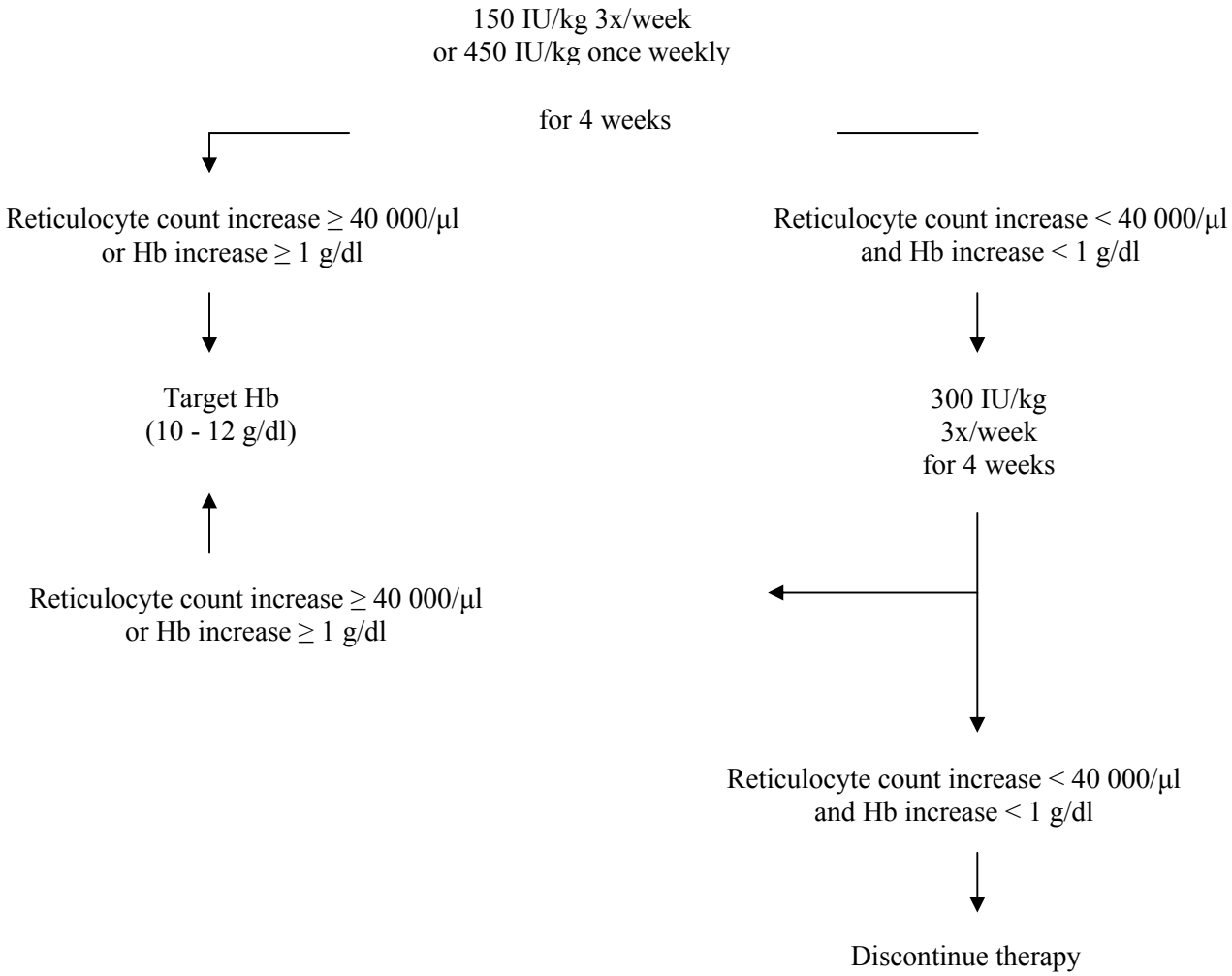
Patients should be monitored closely to ensure that the lowest approved dose of Retacrit is used to provide adequate control of the symptoms of anaemia.

Retacrit 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, Retacrit 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 Retacrit 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 Retacrit therapy at a dose 25% below the previous dose.

Treatment of adult surgery patients in an autologous predonation programme

Retacrit should be given by the intravenous route.

At the time of donating blood, Retacrit 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 Retacrit at a dose of 600 IU/kg body weight 2 times weekly for 3 weeks prior to surgery.

All patients being treated with Retacrit 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 Retacrit therapy.

Treatment of adult patients scheduled for major elective orthopaedic surgery

Retacrit should be administered subcutaneously.

A dose of 600 IU/kg body weight should be administered once weekly for three weeks (on day 21, 14 and 7) prior to surgery and on the day of surgery (day 0). If the lead time before surgery needs to be shortened to less than three weeks, a dose of 300 IU/kg body weight should be given daily for 10 consecutive days prior to surgery, on the day of surgery, and for four days immediately thereafter. When performing haematologic assessments during the preoperative period, if the haemoglobin level reaches 15 g/dl, or higher, administration of Retacrit should be stopped and further doses should not be given.

Iron deficiencies should be treated prior to starting treatment with Retacrit. In addition, all patients should receive adequate iron supplementation (e.g. 200 mg oral elemental iron daily) throughout the course of Retacrit treatment. If possible, iron supplementation should be started prior to treatment with Retacrit, to achieve adequate iron stores.

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.

Retacrit must not be administered by intravenous infusion.
Retacrit 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 Retacrit 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.
- In the indication of major elective orthopaedic surgery: 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 Retacrit. 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 Retacrit. It may be necessary to add or increase anti-hypertensive treatment. If blood pressure cannot be well controlled, Retacrit treatment should be discontinued.

Retacrit 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 Retacrit. 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%.

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 hepatits 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.

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

Patients scheduled for major elective orthopaedic surgery

In patients scheduled for major elective orthopaedic surgery the cause of anaemia should be established and treated, if possible, before the start of Retacrit treatment.

Thrombotic events can be a risk in this population and this possibility should be carefully weighed against the benefit to be derived from the treatment.

Patients 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 Retacrit treatment may be associated with an increased risk of postoperative thrombotic/vascular events cannot be excluded. Therefore, it 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 minimize the risk of developing or worsening of hypertension.

Chronic renal failure patients treated with Retacrit by the subcutaneous route should be monitored regularly for loss of efficacy, defined as absent or decreased response to Retacrit treatment in patients who previously responded to such therapy. This is characterised by a sustained decrease in haemoglobin despite an increase in Retacrit 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 Retacrit 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 Retacrit 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 Retacrit 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 Retacrit) 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 programs, 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 erythropoiesis-stimulating agents (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, Retacrit 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 Retacrit, treatment with Retacrit must not be restarted in this patient at any time. This medicinal product contains phenylalanine which may be harmful for people with phenylketonuria.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. 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.

No data on the effects of epoetin zeta on fertility are available.

4.7 Effects on ability to drive and use machines

Retacrit 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 Retacrit are in line with the safety profile of other authorized erythropoietins. Based on the results from clinical trials with other authorized 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

In this section frequencies of adverse reactions are defined as follows: 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).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Frequencies may vary depending on the indication.

SOC	**Frequency**	**ADR**
Blood and lymphatic system disorders	very rare	Thrombocytosis (see section 4.4)
	Frequency not known	Antibody-mediated erythroblastopenia (PRCA)
Immune system disorders	rare	Hypersensitivity reactions
	very rare	anaphylactic reaction
Nervous system disorders	very common	dizziness (chronic renal failure patients)
		headache (cancer patients)
	common	stroke
		dizziness (cancer patients)
		headache (chronic renal failure patients)
	uncommon	cerebral haemorrhage
	Frequency not known	cerebral infarction
		hypertensive encephalopathy
		transient ischaemic attacks
Eye disorders	Frequency not known	retinal thrombosis
Cardiac disorders	Frequency not known	myocardial infarction
		myocardial ischaemia
Vascular disorders	common	deep vein thrombosis (cancer patients)
		increase in blood pressure
	Frequency not known	aneurysms
		arterial thrombosis
		deep vein thrombosis (chronic renal failure patients)
		hypertensive crisis
Respiratory, thoracic and mediastinal disorders	common	pulmonary embolism (cancer patients)
	uncommon	respiratory tract congestion
	Frequency not known	pulmonary embolism (chronic renal

		failure patients)
Skin and subcutaneous tissue disorders	common	Non-specific skin rashes
	very rare	Angioedema
	Frequency not known	pruritus
Musculoskeletal and connective tissue disorders	very common	joint pains (chronic renal failure patients)
	common	joint pains (cancer patients)
General disorders and administration site conditions	very common	"Flu-like" symptoms (chronic renal failure patients)
		feelings of weakness (chronic renal failure patients)
		tiredness (chronic renal failure patients)
	common	"Flu-like" symptoms (cancer patients)
		feelings of weakness (cancer patients)
		tiredness (cancer patients)
Injury, poisoning and procedural complications	common	clotting of an artificial kidney

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 Retacrit treatment may be associated with an increased risk of postoperative thrombotic/vascular events cannot be excluded.

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 according to their local country requirements.

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

Retacrit 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 leucopoiesis. 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).

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, randomized, 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 statisfactorily 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 perfomed 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).

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

Retacrit 2 000 IU/0.6 ml solution for injection in pre-filled syringe
Pre-filled syringe Type I glass with a fixed steel injection needle and a plunger stopper with PTFE coating with or without a needle guard or needle-trap device.
Each pre-filled syringe contains 0.6 ml solution.
Each pack contains 1 or 6 pre-filled syringes.

Retacrit 4 000 IU/0.4 ml solution for injection in pre-filled syringe
Pre-filled syringe Type I glass with a fixed steel injection needle and a plunger stopper with PTFE coating with or without a needle guard or needle-trap device.
Each pre-filled syringe contains 0.4 ml solution.
Each pack contains 1 or 6 pre-filled syringes.

Retacrit 10 000 IU/1 ml solution for injection in pre-filled syringe
Pre-filled syringe Type I glass with a fixed steel injection needle and a plunger stopper with PTFE coating with or without a needle guard or needle-trap device.
Each pre-filled syringe contains 1 ml solution.
Each pack contains 1 or 6 pre-filled syringes.

Retacrit 40 000 IU/1 ml solution for injection in pre-filled syringe
Pre-filled syringe Type I glass with a fixed steel injection needle and a plunger stopper with PTFE coating with or without a needle guard or needle-trap device.
Each pre-filled syringe contains 1 ml solution.
Each pack contains 1, 4 or 6 pre-filled syringes.
Multipacks contain 4 (4 x 1) pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions for Retacrit:
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.

Retacrit 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

Hospira UK Limited
Horizon
Honey Lane
Hurley
Maidenhead
SL6 6RJ
UK

Manufacturing Site

Rovi Contract Manufacturing S.L.
Madrid, Spain

Site responsible for Batch release:

Hospira Zagreb d.o.o, Croatia

10. DATE OF REVISION OF THE TEXT

September 2017