ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Abseamed 1 000 IU/0.5 mL solution for injection in a pre-filled syringe
Abseamed 2 000 IU/1 mL solution for injection in a pre-filled syringe
Abseamed 3 000 IU/0.3 mL solution for injection in a pre-filled syringe
Abseamed 4 000 IU/0.4 mL solution for injection in a pre-filled syringe
Abseamed 5 000 IU/0.5 mL solution for injection in a pre-filled syringe
Abseamed 6 000 IU/0.6 mL solution for injection in a pre-filled syringe
Abseamed 7 000 IU/0.7 mL solution for injection in a pre-filled syringe
Abseamed 8 000 IU/0.8 mL solution for injection in a pre-filled syringe
Abseamed 9 000 IU/0.9 mL solution for injection in a pre-filled syringe
Abseamed 10 000 IU/1 mL solution for injection in a pre-filled syringe
Abseamed 20 000 IU/0.5 mL solution for injection in a pre-filled syringe
Abseamed 30 000 IU/0.75 mL solution for injection in a pre-filled syringe
Abseamed 40 000 IU/1 mL solution for injection in a pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Abseamed 1 000 IU/0.5 mL solution for injection in a pre-filled syringe
Each mL of solution contains 2 000 IU of epoetin alfa* corresponding to 16.8 micrograms per mL
A pre-filled syringe of 0.5 mL contains 1 000 international units (IU) corresponding to 8.4 micrograms epoetin alfa. *

Abseamed 2 000 IU/1 mL solution for injection in a pre-filled syringe
Each mL of solution contains 2 000 IU of epoetin alfa* corresponding to 16.8 micrograms per mL
A pre-filled syringe of 1 mL contains 2 000 international units (IU) corresponding to 16.8 micrograms epoetin alfa. *

Abseamed 3 000 IU/0.3 mL solution for injection in a pre-filled syringe
Each mL of solution contains 10 000 IU of epoetin alfa* corresponding to 84.0 micrograms per mL
A pre-filled syringe of 0.3 mL contains 3 000 international units (IU) corresponding to 25.2 micrograms epoetin alfa. *

Abseamed 4 000 IU/0.4 mL solution for injection in a pre-filled syringe
Each mL of solution contains 10 000 IU of epoetin alfa* corresponding to 84.0 micrograms per mL
A pre-filled syringe of 0.4 mL contains 4 000 international units (IU) corresponding to 33.6 micrograms epoetin alfa. *

Abseamed 5 000 IU/0.5 mL solution for injection in a pre-filled syringe
Each mL of solution contains 10 000 IU of epoetin alfa* corresponding to 84.0 micrograms per mL
A pre-filled syringe of 0.5 mL contains 5 000 international units (IU) corresponding to 42.0 micrograms epoetin alfa. *

Abseamed 6 000 IU/0.6 mL solution for injection in a pre-filled syringe
Each mL of solution contains 10 000 IU of epoetin alfa* corresponding to 84.0 micrograms per mL
A pre-filled syringe of 0.6 mL contains 6 000 international units (IU) corresponding to 50.4 micrograms epoetin alfa. *

Abseamed 7 000 IU/0.7 mL solution for injection in a pre-filled syringe
Each mL of solution contains 10 000 IU of epoetin alfa* corresponding to 84.0 micrograms per mL
A pre-filled syringe of 0.7 mL contains 7 000 international units (IU) corresponding to 58.8 micrograms epoetin alfa. *

Abseamed 8 000 IU/0.8 mL solution for injection in a pre-filled syringe
Each mL of solution contains 10 000 IU of epoetin alfa* corresponding to 84.0 micrograms per mL
A pre-filled syringe of 0.8 mL contains 8 000 international units (IU) corresponding to 67.2 micrograms epoetin alfa. *

Abseamed 9 000 IU/0.9 mL solution for injection in a pre-filled syringe
Each mL of solution contains 10 000 IU of epoetin alfa* corresponding to 84.0 micrograms per mL
A pre-filled syringe of 0.9 mL contains 9 000 international units (IU) corresponding to 75.6 micrograms epoetin alfa. *

Abseamed 10 000 IU/1 mL solution for injection in a pre-filled syringe
Each mL of solution contains 10 000 IU of epoetin alfa* corresponding to 84.0 micrograms per mL
A pre-filled syringe of 1 mL contains 10 000 international units (IU) corresponding to 84.0 micrograms epoetin alfa. *

Abseamed 20 000 IU/0.5 mL solution for injection in a pre-filled syringe
Each mL of solution contains 40 000 IU of epoetin alfa* corresponding to 336.0 micrograms per mL
A pre-filled syringe of 0.5 mL contains 20 000 international units (IU) corresponding to 168.0 micrograms epoetin alfa. *

Abseamed 30 000 IU/0.75 mL solution for injection in a pre-filled syringe
Each mL of solution contains 40 000 IU of epoetin alfa* corresponding to 336.0 micrograms per mL
A pre-filled syringe of 0.75 mL contains 30 000 international units (IU) corresponding to 252.0 micrograms epoetin alfa. *

Abseamed 40 000 IU/1 mL solution for injection in a pre-filled syringe
Each mL of solution contains 40 000 IU of epoetin alfa* corresponding to 336.0 micrograms per mL
A pre-filled syringe of 1 mL contains 40 000 international units (IU) corresponding to 336.0 micrograms epoetin alfa. *

* Produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled syringe (injection)
Clear, colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- in adults and children aged 1 to 18 years on haemodialysis and adult patients on peritoneal dialysis (see section 4.4).
- in adults with renal insufficiency not yet undergoing dialysis for the treatment of severe anaemia of renal origin accompanied by clinical symptoms in patients (see section 4.4).

Abseamed 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.

Abseamed 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 [Hb] 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).

Abseamed 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 or 6.2 to 8.1 mmol/L) who do not have an autologous predonation programme available and with expected moderate blood loss (900 to 1 800 mL).

Abseamed is indicated for the treatment of 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 Abseamed has to be initiated under the supervision of physicians experienced in the management of patients with the above indications.

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 alfa, and when deciding to increase the dose. In order to ensure optimum response to epoetin alfa, 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). Abseamed 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 Abseamed 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 Abseamed therapy at a dose 25% below the previous dose.

Patients should be monitored closely to ensure that the lowest approved effective dose of Abseamed 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 erythropoiesis-stimulating agent (ESA) doses in patients with CRF. 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 Abseamed 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 Abseamed 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, Abseamed 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 Abseamed 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.

Abseamed 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, Abseamed 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) is described below.

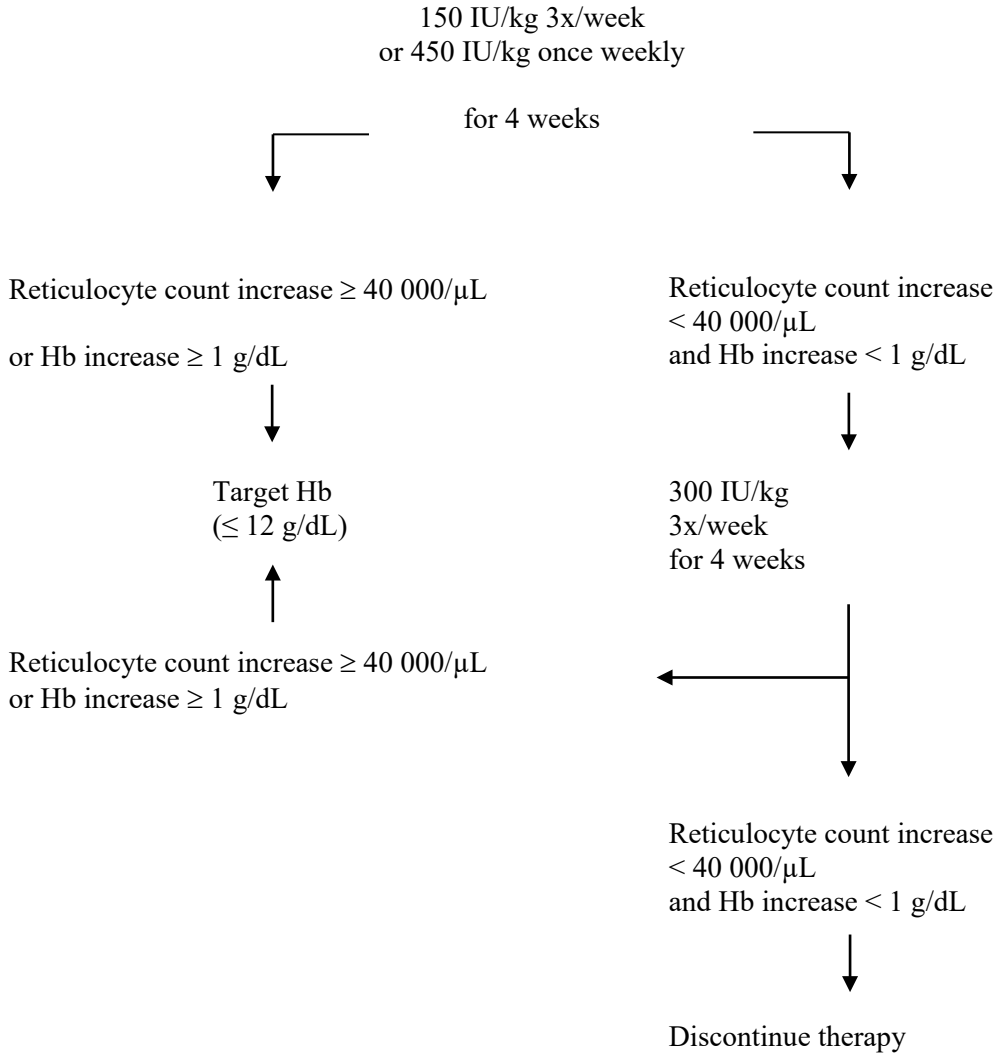
- If the haemoglobin concentration has increased by at least 1 g/dL (0.62 mmol/L) or the reticulocyte count has increased ≥ 40 000 cells/µL above baseline after 4 weeks of treatment, the dose should remain at 150 IU/kg 3 times per week or 450 IU/kg once weekly.
- If the haemoglobin concentration increase 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 (6.2 to 7.5 mmol/L)

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 Abseamed 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 Abseamed therapy at a dose 25% below the previous dose.

The recommended dosing regimen is described in the following diagram:



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

Epoetin alfa 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 Abseamed 600 IU/kg intravenously, 2 times per week for 3 weeks prior to surgery. Abseamed 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 Abseamed 600 IU/kg, administered subcutaneously weekly for three weeks (days -21, -14 and -7) prior to surgery and on the day of surgery (day 0).

In cases where there is a medical need to shorten the lead time before surgery to less than three weeks, Abseamed 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 (9.38 mmol/L), or higher, during the preoperative period, administration of Abseamed should be stopped and further dosages should not be administered.

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

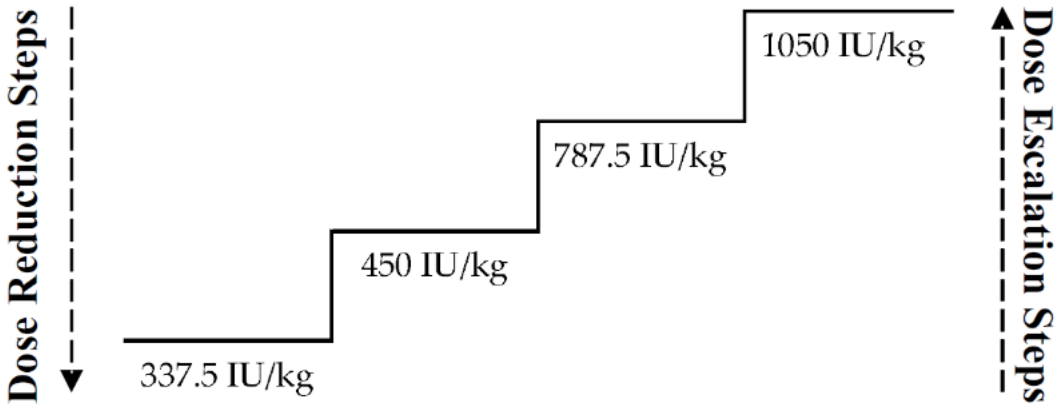
Abseamed should be administered to patients with symptomatic anaemia (e.g. haemoglobin concentration ≤ 10 g/dL (6.2 mmol/L)).

The recommended starting dose is Abseamed 450 IU/kg (maximum total dose is 40 000 IU) administered 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: Epoetin alfa 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.

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). Abseamed 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 Abseamed is used to provide adequate control of anaemia and of the symptoms of anaemia.

Treatment with Abseamed 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 alfa in chronic renal failure patients with anaemia before initiation of dialysis or on peritoneal dialysis have not been established. Currently available data for subcutaneous use of epoetin alfa in these populations are described in section 5.1 but no recommendation on posology can be made.

Treatment of paediatric patients with chemotherapy-induced anaemia
The safety and efficacy of epoetin alfa in paediatric patients receiving chemotherapy have not been established (see section 5.1).

Treatment of paediatric surgery patients in an autologous predonation programme
The safety and efficacy of epoetin alfa 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 alfa 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 Abseamed syringe to stand until it reaches room temperature. This usually takes between 15 and 30 minutes.
As with any other injectable product, check that there are no particles in the solution or change in colour. Abseamed is a sterile but unpreserved product and is for single use only. Administer the amount required.

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 Abseamed by the intravenous route is preferable.

Where intravenous access is not readily available (patients not yet undergoing dialysis and peritoneal dialysis patients) Abseamed may be administered as a subcutaneous injection.

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

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

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

Treatment of adult patients with low- or intermediate-1-risk MDS
Abseamed 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 Abseamed 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 "flu-like" symptoms (see section 4.8).

Do not administer Abseamed by intravenous infusion or in conjunction with other medicinal product solutions (please refer to section 6.6 for further information).

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 Abseamed subcutaneously themselves, instruction as to the proper dosage and administration should be provided.

Graduation rings
The syringe contains graduation rings to provide for the administration of a part of the dose (see section 6.6). However the product is for single use only. Only one dose of Abseamed from each syringe should be taken.

"Instructions on how to inject Abseamed yourself" can be found at the end of the package leaflet.

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 should not receive Abseamed or any other erythropoietin (see section 4.4).

- Uncontrolled hypertension.

- All contraindications associated with autologous blood predonation programmes should be respected in patients being supplemented with Abseamed.

The use of Abseamed 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

Traceablility

In order to improve the traceability of erythropoiesis-stimulating agents (ESAs), the trade name and the batch number 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.

General

In all patients receiving epoetin alfa, blood pressure should be closely monitored and controlled as necessary. Epoetin alfa 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 alfa 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 alfa 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 4.8).

Epoetin alfa 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 alfa should be used with caution in patients with chronic liver failure. The safety of epoetin alfa 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 alfa 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 alfa. 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 alfa, 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 alfa, adequate iron stores should be assured and iron supplementation should be administered if necessary (see section 4.2). For the selection of the best treatment option according to the patient's needs, current treatment guidelines on iron supplementation in combination with dose instructions approved and outlined in the SmPC of the iron medication should be followed:

- For chronic renal failure patients, iron supplementation is recommended if serum ferritin levels are below 100 ng/mL.

- For cancer patients, iron supplementation is recommended if transferrin saturation is below 20%.

- For patients in an autologous predonation programme, iron supplementation should be administered several weeks prior to initiating the autologous predeposit in order to achieve high iron stores prior to starting epoetin alfa therapy, and throughout the course of epoetin alfa therapy.

- For patients scheduled for major elective orthopaedic surgery, iron supplementation should be administered throughout the course of epoetin alfa therapy. If possible, iron supplementation should be initiated prior to starting epoetin alfa therapy to achieve adequate iron stores.

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

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, Abseamed 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 Abseamed, treatment with Abseamed must not be restarted in this patient at any time.

Pure Red Cell Aplasia (PRCA)

Antibody-mediated PRCA has been reported after months to years of epoetin alfa treatment. Cases have also been reported in patients with hepatitis C treated with interferon and ribavirin, when ESAs are used concomitantly. Epoetin alfa 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 or 0.62 to 1.25 mmol/L 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 alfa 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 alfa 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 studies, 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 studies 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 Abseamed 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 section 4.2 and 5.1).

Chronic renal failure patients treated with epoetin alfa by the subcutaneous route should be monitored regularly for loss of efficacy, defined as absent or decreased response to epoetin alfa treatment in patients who previously responded to such therapy. This is characterised by a sustained decrease in haemoglobin despite an increase in epoetin alfa dosage (see section 4.8).

Some patients with more extended dosing intervals (greater than once weekly) of epoetin alfa may not maintain adequate haemoglobin levels (see section 5.1) and may require an increase in epoetin alfa 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 alfa 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 alfa 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 alfa 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 alfa 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 (RBC) 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 epoetin alfa and other ESAs have been associated with decreased locoregional tumour control or decreased overall survival:

- decreased locoregional control in patients with advanced head and neck cancer receiving radiation therapy when administered to achieve a haemoglobin concentration level 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 achieve a haemoglobin concentration range of 12 to 14 g/dL (7.5 to 8.7 mmol/L),

- increased risk of death when administered to achieve a haemoglobin concentration level 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,

- an observed 9% increase in risk for progress of disease (PD) or death in the epoetin alfa plus standard of care group from a primary analysis and a 15% increased risk that cannot be statistically ruled out in patients with metastatic breast cancer receiving chemotherapy when administered to achieve a haemoglobin concentration range of 10 to 12 g/dL (6.2 to 7.5 mmol/L).

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 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 (see section 5.1).

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 alfa 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 deep venous thrombosis (DVTs). Moreover, in patients with a baseline haemoglobin of > 13 g/dL (> 8.1 mmol/L), the possibility that epoetin alfa treatment may be associated with an increased risk of postoperative thrombotic/vascular events cannot be excluded. Therefore, epoetin alfa should not be used in patients with baseline haemoglobin > 13 g/dL (> 8.1 mmol/L).

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

No evidence exists that indicates that treatment with epoetin alfa alters the metabolism of other medicinal products.
Medicinal products that decrease erythropoiesis may decrease the response to epoetin alfa.

Since cyclosporin is bound by RBCs there is potential for a medicinal product interaction. If epoetin alfa 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 alfa and granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (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 alfa with trastuzumab 6 mg/kg had no effect on the pharmacokinetics of trastuzumab.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of epoetin alfa in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Consequently, epoetin alfa should be used in pregnancy only if the potential benefit outweighs the potential risk to the foetus. The use of epoetin alfa is not recommended in pregnant surgical patients participating in an autologous blood predonation programme.

Breast-feeding

It is unknown whether exogenous epoetin alfa is excreted in human milk. A risk to the newborns/infants cannot be excluded.
Epoetin alfa should be used with caution in nursing women. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy with epoetin alfa taking into account the benefit of breast-feeding for the child and the benefit of epoetin alfa therapy for the woman.

The use of epoetin alfa is not recommended in lactating surgical patients participating in an autologous blood predonation programme.

Fertility

There are no studies assessing the potential effect of epoetin alfa on male or female fertility.

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

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse drug reaction during treatment with epoetin alfa is a dose-dependent 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 studies 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).

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 CRF studies (2 studies in pre-dialysis [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 studies 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 (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], Thrombocythaemia	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	Common

MedDRA System Organ Classification (SOC)	Adverse Reaction (Preferred Term Level)	Frequency
	peripheral	
	Medicinal product ineffective[3]	Not known
Investigations	Anti-erythropoietin 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

Hypersensitivity reactions, including cases of rash (including urticaria), anaphylactic reactions, and angioneurotic oedema have been reported (see section 4.4).

SCARs including SJS and TEN, which can be life-threatening or fatal, have been reported in association with epoetin treatment (see section 4.4).

Hypertensive crisis with encephalopathy and seizures, requiring the immediate attention of a physician and intensive medical care, have occurred also during epoetin alfa 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 < 1/10 000 cases per patient year after months to years of treatment with epoetin alfa (see section 4.4). More cases have been reported with subcutaneous route of administration, compared with the intravenous route.

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).

Paediatric population with chronic renal failure on haemodialysis
The exposure of paediatric patients with chronic renal failure on haemodialysis in clinical studies and post-marketing experience is limited. No paediatric-specific adverse reactions not mentioned previously in the table above, or any that were not consistent with the underlying disease were 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 reporting system listed in Appendix V.

4.9 Overdose

The therapeutic margin of epoetin alfa is very wide. Overdosage of epoetin alfa 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.

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

Mechanism of action

Erythropoietin (EPO) is a glycoprotein hormone produced primarily by the kidney in response to hypoxia and is the key regulator of RBC production. EPO is involved in all phases of erythroid development, and has its principal effect at the level of erythroid precursors. After EPO binds to its cell surface receptor, it activates signal transduction pathways that interfere with apoptosis and stimulates erythroid cell proliferation.
Recombinant human EPO (epoetin alfa), expressed in Chinese hamster ovary cells, has a 165 amino acid sequence identical to that of human urinary EPO; the 2 are indistinguishable on the basis of functional assays. The apparent molecular weight of erythropoietin is 32 000 to 40 000 dalton.

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.

Pharmacodynamic effects

Healthy volunteers
After single doses (20 000 to 160 000 IU subcutaneously) of epoetin alfa, a dose-dependent response was observed for the pharmacodynamic markers investigated including: reticulocytes, RBCs, and haemoglobin. A defined concentration-time profile with peak and return to baseline was observed for changes in percent reticulocytes. A less defined profile was observed for RBCs and haemoglobin. In general, all pharmacodynamic markers increased in a linear manner with dose reaching a maximum response at the highest dose levels.

Further pharmacodynamic studies explored 40 000 IU once weekly versus 150 IU/kg 3 times per week. Despite differences in concentration-time profiles the pharmacodynamic response (as measured by changes in percent reticulocytes, haemoglobin, and total RBCs) was similar between these regimens. Additional studies compared the 40 000 IU once-weekly regimen of epoetin alfa with biweekly doses ranging from 80 000 to 120 000 IU subcutaneously. Overall, based on the results of these pharmacodynamic studies in healthy subjects, the 40 000 IU once-weekly dosing regimen seems to be more efficient in producing RBCs than the biweekly regimens despite an observed similarity in reticulocyte production in the once-weekly and biweekly regimens.

Chronic renal failure
Epoetin alfa has been shown to stimulate erythropoiesis in anaemic patients with CRF, including dialysis and pre-dialysis patients. The first evidence of a response to epoetin alfa is an increase in the reticulocyte count within 10 days, followed by increases in the red cell count, haemoglobin and haematocrit, usually within 2 to 6 weeks. The haemoglobin response varies between patients and may be impacted by iron stores and the presence of concurrent medical problems.

Chemotherapy-induced anaemia
Epoetin alfa administered 3 times per week or once weekly has been shown to increase haemoglobin and decrease transfusion requirements after the first month of therapy in anaemic cancer patients receiving chemotherapy.

In a study comparing the 150 IU/kg, 3 times per week and 40 000 IU, once-weekly dosing regimens in healthy subjects and in anaemic cancer subjects the time profiles of changes in percent reticulocytes, haemoglobin, and total red blood cells were similar between the two dosing regimens in both healthy and anaemic cancer subjects. The AUCs of the respective pharmacodynamic parameters were similar between the 150 IU/kg, 3 times per week and 40 000 IU, once-weekly dosing regimens in healthy subjects and also in anaemic cancer subjects.

Adult surgery patients in an autologous predonation programme
Epoetin alfa has been shown to stimulate red blood cell production in order to augment autologous blood collection, and to limit the decline in haemoglobin in adult patients scheduled for major elective surgery who are not expected to predeposit their complete perioperative blood needs. The greatest effects are observed in patients with low haemoglobin (≤ 13 g/dL).

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

Chronic renal failure
Epoetin alfa has been studied in clinical studies in adult anaemic CRF patients, including haemodialysis and pre-dialysis patients, to treat anaemia and maintain haematocrit within a target concentration range of 30 to 36%.

In clinical studies at starting doses of 50 to 150 IU/kg, three times per week, approximately 95% of all patients responded with a clinically significant increase in haematocrit. After approximately two months of therapy, virtually all patients were transfusion-independent. Once the target haematocrit was achieved, the maintenance dose was individualised for each patient.

In the three largest clinical studies conducted in adult patients on dialysis, the median maintenance dose necessary to maintain the haematocrit between 30 to 36% was approximately 75 IU/kg given 3 times per week.

In a double-blind, placebo-controlled, multicentre, quality of life study in CRF patients on haemodialysis, clinically and statistically significant improvement was shown in the patients treated with epoetin alfa compared to the placebo group when measuring fatigue, physical symptoms, relationships and depression (Kidney Disease Questionnaire) after six months of therapy. Patients from the group treated with epoetin alfa were also enrolled in an open-label extension study which demonstrated improvements in their quality of life that were maintained for an additional 12 months.

Adult patients with renal insufficiency not yet undergoing dialysis
In clinical studies conducted in patients with CRF not on dialysis treated with epoetin alfa, the average duration of therapy was nearly five months. These patients responded to epoetin alfa therapy in a manner similar to that observed in patients on dialysis. Patients with CRF not on dialysis demonstrated a dose-dependent and sustained increase in haematocrit when epoetin alfa was administered by either an intravenous or subcutaneous route. Similar rates of rise of haematocrit were noted when epoetin alfa was administered by either route. Moreover, epoetin alfa doses of 75 to 150 IU/kg per week have been shown to maintain haematocrits of 36 to 38% for up to six months.

In 2 studies with extended interval dosing of epoetin alfa (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).

A randomised prospective study evaluated 1 432 anaemic chronic renal failure patients who were not undergoing dialysis. Patients were assigned to epoetin alfa treatment targeting a maintenance haemoglobin level of 13.5 g/dL (higher than the recommended haemoglobin concentration level) or 11.3 g/dL. A major cardiovascular event (death, myocardial infarction, stroke or hospitalisation for congestive heart failure) occurred among 125 (18%) of the 715 patients in the higher haemoglobin group compared to 97 (14%) among the 717 patients in the lower haemoglobin group (hazard ratio [HR] 1.3, 95% CI: 1.0, 1.7, p = 0.03).

Pooled post-hoc analyses of clinical studies of ESAs have been performed in chronic renal failure 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 section 4.2 and section 4.4).

Treatment of patients with chemotherapy-induced anaemia
Epoetin alfa has been studied in clinical studies in adult anaemic cancer patients with lymphoid and solid tumors, and patients on various chemotherapy regimens, including platinum and non-platinum-containing regimens. In these studies, epoetin alfa administered 3 times per week and once weekly has been shown to increase haemoglobin and decrease transfusion requirements after the first month of therapy in anaemic cancer patients. In some studies, the double-blind phase was followed by an open-label phase during which all patients received epoetin alfa and a maintenance of effect was observed.

Available evidence suggests patients with haematological malignancies and solid tumours respond equivalently to epoetin alfa therapy, and that patients with or without tumour infiltration of the bone marrow respond equivalently to epoetin alfa therapy. Comparable intensity of chemotherapy in the epoetin alfa and placebo groups in the chemotherapy studies was demonstrated by a similar area under the neutrophil time curve in patients treated with epoetin alfa and placebo-treated patients, as well as by a similar proportion of patients in groups treated with epoetin alfa and placebo-treated groups whose absolute neutrophil counts fell below 1 000 and 500 cells/µL.

In a prospective, randomised, double-blind, placebo-controlled study 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 studies failed to show a significant improvement in quality of life parameters on the EORTC-QLQ-C30 scale or CLAS, respectively. 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 ESAs are not indicated: anaemia in patients with cancer not receiving chemotherapy, and head and neck cancer patients receiving radiotherapy. The desired haemoglobin concentration level in two studies was > 13 g/dL (8.1 mmol/L); in the remaining three studies it was 12 to 14 g/dL (7.5 to 8.7 mmol/L). 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 studies 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 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 studies 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 studies 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 studies 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).

A randomised, open-label, multicentre study was conducted in 2 098 anaemic women with metastatic breast cancer, who received first line or second line chemotherapy. This was a non inferiority study designed to rule out a 15% risk increase in tumour progression or death of epoetin alfa plus standard of care as compared with standard of care alone. At the time of clinical data cutoff, the median progression free survival (PFS) per investigator assessment of disease progression was 7.4 months in each arm (HR 1.09, 95% CI: 0.99, 1.20), indicating the study objective was not met. Significantly fewer patients received RBC transfusions in the epoetin alfa plus standard of care arm (5.8% versus 11.4%); however, significantly more patients had thrombotic vascular events in the epoetin alfa plus standard of care arm (2.8% versus 1.4%). At the final analysis, 1 653 deaths were reported. Median overall survival in the epoetin alfa plus standard of care group was 17.8 months compared with 18.0 months in the standard of care alone group (HR 1.07, 95% CI: 0.97, 1.18). The median time to progression (TTP) based on investigator-determined progressive disease (PD) was 7.5 months in the epoetin alfa plus standard of care group and 7.5 months in the standard of care group (HR 1.099, 95% CI: 0.998, 1.210). The median TTP based on IRC-determined PD was 8.0 months in the epoetin alfa plus standard of care group and 8.3 months in the standard of care group (HR 1.033, 95% CI: 0.924, 1.156).

Autologous predonation programme
The effect of epoetin alfa in facilitating autologous blood donation in patients with low haematocrits (≤ 39% and no underlying anaemia due to iron deficiency) scheduled for major orthopaedic surgery was evaluated in a double-blind, placebo-controlled study conducted in 204 patients, and a single-blind placebo controlled study in 55 patients.

In the double-blind study, patients were treated with epoetin alfa 600 IU/kg or placebo intravenously once daily every 3 to 4 days over 3 weeks (total 6 doses). On average, patients treated with epoetin alfa were able to predeposit significantly more units of blood (4.5 units) than placebo-treated patients (3.0 units).

In the single-blind study, patients were treated with epoetin alfa 300 IU/kg or 600 IU/kg or placebo intravenously once daily every 3 to 4 days over 3 weeks (total 6 doses). Patients treated with epoetin alfa were also able to predeposit significantly more units of blood (epoetin alfa 300 IU/kg = 4.4 units; epoetin alfa 600 IU/kg = 4.7 units) than placebo-treated patients (2.9 units).

Epoetin alfa therapy reduced the risk of exposure to allogeneic blood by 50% compared to patients not receiving epoetin alfa.

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 study 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 study 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	
Total (N)[b]	Epoetin alfa	Placebo
	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.

Paediatric population

Chronic renal failure
Epoetin alfa was evaluated in an open-label, non-randomised, open dose-range, 52-week clinical study in paediatric CRF patients undergoing haemodialysis. The median age of patients enrolled in the study was 11.6 years (range 0.5 to 20.1 years).

Epoetin alfa was administered at 75 IU/kg/week intravenously in 2 or 3 divided doses post-dialysis, titrated by 75 IU/kg/week at intervals of 4 weeks (up to a maximum of 300 IU/kg/week), to achieve a 1 g/dL/month increase in haemoglobin. The desired haemoglobin concentration range was 9.6 to 11.2 g/dL. Eighty-one percent of patients achieved the haemoglobin concentration level. The median time to target was 11 weeks and the median dose at target was 150 IU/kg/week. Of the patients who achieved the target, 90% did so on a 3 times-per-week dosing regimen.

After 52 weeks, 57% of patients remained in the study, receiving a median dose of 200 IU/kg/week.

Clinical data with subcutaneous administration in children are limited. In 5 small, open label, uncontrolled studies (number of patients ranged from 9-22, total N = 72), epoetin alfa has been administered subcutaneously in children at starting doses of 100 IU/kg/week to 150 IU/kg/week with the possibility to increase up to 300 IU/kg/week. In these studies, most were predialysis patients (N = 44), 27 patients were on peritoneal dialysis and 2 were on haemodialysis with age ranging from 4 months to 17 years. Overall, these studies have methodological limitations but treatment was associated with positive trends towards higher haemoglobin levels. No unexpected adverse reactions were reported (see section 4.2).

Chemotherapy-induced anaemia

Epoetin alfa 600 IU/kg (administered intravenously or subcutaneously once weekly) has been evaluated in a randomised, double-blind, placebo-controlled, 16-week study and in a randomised, controlled, open-label, 20-week study in anaemic paediatric patients receiving myelosuppressive chemotherapy for the treatment of various childhood non-myeloid malignancies.

In the 16-week study (n = 222), in the epoetin alfa-treated patients there was no statistically significant effect on patient-reported or parent-reported Paediatric Quality of Life Inventory or Cancer Module scores compared with placebo (primary efficacy endpoint). In addition, there was no statistical difference between the proportion of patients requiring pRBC transfusions between the Epoetin alfa group and placebo.

In the 20-week study (n = 225), no significant difference was observed in the primary efficacy endpoint, i.e. the proportion of patients who required a RBC transfusion after Day 28 (62% of epoetin alfa patients versus 69% of standard therapy patients).

5.2 Pharmacokinetic properties

Absorption
Following subcutaneous injection, serum levels of epoetin alfa reach a peak between 12 and 18 hours post-dose. There was no accumulation after multiple dose administration of 600 IU/kg administered subcutaneously weekly.

The absolute bioavailability of subcutaneous injectable epoetin alfa is approximately 20% in healthy subjects.

Distribution
The mean volume of distribution was 49.3 mL/kg after intravenous doses of 50 and 100 IU/kg in healthy subjects. Following intravenous administration of epoetin alfa in subjects with chronic renal failure, the volume of distribution ranged from 57-107 mL/kg after single dosing (12 IU/kg) to 42–64 mL/kg after multiple dosing (48–192 IU/kg), respectively. Thus, the volume of distribution is slightly greater than the plasma space.

Elimination
The half-life of epoetin alfa following multiple dose intravenous administration is approximately 4 hours in healthy subjects.
The half-life for the subcutaneous route is estimated to be approximately 24 hours in healthy subjects.

The mean CL/F for the 150 IU/kg 3 times-per-week and 40,000 IU once-weekly regimens in healthy subjects were 31.2 and 12.6 mL/h/kg, respectively. The mean CL/F for the 150 IU/kg, 3 times-per-week and 40 000 IU, once-weekly regimens in the anaemic cancer subjects were 45.8 and 11.3 mL/h/kg, respectively. In most anaemic subjects with cancer receiving cyclic chemotherapy, CL/F was lower after subcutaneous doses of 40 000 IU once weekly and 150 IU/kg, 3 times-per-week compared with the values for healthy subjects.

Linearity/Non-linearity
In healthy subjects, a dose-proportional increase in serum epoetin alfa concentrations was observed after intravenous administration of 150 and 300 IU/kg, 3 times per week. Administration of single doses of 300 to 2 400 IU/kg subcutaneous epoetin alfa resulted in a linear relationship between mean C_{max} and dose and between mean AUC and dose. An inverse relationship between apparent clearance and dose was noted in healthy subjects.

In studies to explore extending the dosing interval (40 000 IU once weekly and 80 000, 100 000, and 120 000 IU biweekly), a linear but non-dose-proportional relationship was observed between mean C_{max} and dose, and between mean AUC and dose at steady state.

Pharmacokinetic/pharmacodynamic relationships
Epoetin alfa exhibits a dose-related effect on haematological parameters which is independent of route of administration.

Paediatric population
A half-life of approximately 6.2 to 8.7 hours has been reported in paediatric subjects with chronic renal failure following multiple dose intravenous administration of epoetin alfa. The pharmacokinetic profile of epoetin alfa in children and adolescents appears to be similar to that of adults.

Pharmacokinetic data in neonates is limited.

A study of 7 preterm very low birth weight neonates and 10 healthy adults given i.v. erythropoietin suggested that distribution volume was approximately 1.5 to 2 times higher in the preterm neonates than in the healthy adults, and clearance was approximately 3 times higher in the preterm neonates than in healthy adults.

Renal impairment
In chronic renal failure patients, the half-life of intravenously administered epoetin alfa is slightly prolonged, approximately 5 hours, compared to healthy subjects.

5.3 Preclinical safety data

In repeated dose toxicological studies in dogs and rats, but not in monkeys, epoetin alfa 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 epoetin alfa for 3 years compared to a matched control group of dialysis patients who had not been treated with epoetin alfa.

Epoetin alfa does not induce bacterial gene mutation (Ames Test), chromosomal aberrations in mammalian cells, micronuclei in mice, or gene mutation at the HGPRT locus.

Long-term carcinogenicity studies have not been carried out. Conflicting reports in the literature, based on *in vitro* findings from human tumour samples, suggest erythropoietins may play a role as tumour proliferators. This is of uncertain significance in the clinical situation.

In cell cultures of human bone marrow cells, epoetin alfa stimulates erythropoiesis specifically and does not affect leucopoiesis. Cytotoxic actions of epoetin alfa on bone marrow cells could not be detected.

In animal studies, epoetin alfa 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, and the significance to humans is unknown given therapeutic dose levels.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate dihydrate
Disodium phosphate dihydrate
Sodium chloride
Glycine
Polysorbate 80
Water for injections
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store and transport refrigerated (2 °C to 8 °C). This temperature range should be closely maintained until administration to the patient.
For the purpose of ambulatory use, the medicinal product may be taken out of the refrigerator, without being replaced, for a maximum period of 3 days at a temperature not above 25 °C. If the medicinal product has not been used at the end of this period, it should be disposed of.

Do not freeze or shake.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Pre-filled syringes (glass type I), with or without a needle safety guard, with plunger stopper (Teflon-faced rubber) sealed in a blister.

Abseamed 1 000 IU/0.5 mL solution for injection in a pre-filled syringe
Each syringe contains 0.5 mL of solution for injection.
Pack of 1 or 6 syringes.

Abseamed 2 000 IU/1 mL solution for injection in a pre-filled syringe
Each syringe contains 1 mL of solution for injection.
Pack of 1 or 6 syringes.

Abseamed 3 000 IU/0.3 mL solution for injection in a pre-filled syringe
Each syringe contains 0.3 mL of solution for injection.
Pack of 1 or 6 syringes.

Abseamed 4 000 IU/0.4 mL solution for injection in a pre-filled syringe
Each syringe contains 0.4 mL of solution for injection.
Pack of 1 or 6 syringes.

Abseamed 5 000 IU/0.5 mL solution for injection in a pre-filled syringe
Each syringe contains 0.5 mL of solution for injection.
Pack of 1 or 6 syringes.

Abseamed 6 000 IU/0.6 mL solution for injection in a pre-filled syringe
Each syringe contains 0.6 mL of solution for injection.
Pack of 1 or 6 syringes.

Abseamed 7 000 IU/0.7 mL solution for injection in a pre-filled syringe
Each syringe contains 0.7 mL of solution for injection.
Pack of 1 or 6 syringes.

Abseamed 8 000 IU/0.8 mL solution for injection in a pre-filled syringe
Each syringe contains 0.8 mL of solution for injection.
Pack of 1 or 6 syringes.

Abseamed 9 000 IU/0.9 mL solution for injection in a pre-filled syringe
Each syringe contains 0.9 mL of solution for injection.
Pack of 1 or 6 syringes.

Abseamed 10 000 IU/1 mL solution for injection in a pre-filled syringe
Each syringe contains 1 mL of solution for injection.
Pack of 1 or 6 syringes.

Abseamed 20 000 IU/0.5 mL solution for injection in a pre-filled syringe
Each syringe contains 0.5 mL of solution for injection.
Pack of 1, 4 or 6 syringes.

Abseamed 30 000 IU/0.75 mL solution for injection in a pre-filled syringe
Each syringe contains 0.75 mL of solution for injection.
Pack of 1, 4 or 6 syringes.

Abseamed 40 000 IU/1 mL solution for injection in a pre-filled syringe
Each syringe contains 1 mL of solution for injection.
Pack of 1, 4 or 6 syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Abseamed should not be used and discarded
- if the liquid is coloured or you can see particles floating in it,
- if the seal is broken,
- if you know, or think that it may have been accidentally frozen, or
- if there has been a refrigerator failure.

The pre-filled syringes are ready to use (see section 4.2). The pre-filled syringe should not be shaken. Syringes are embossed with graduation rings in order to enable partial use if required. Each graduation ring corresponds to a volume of 0.1 mL. The product is for single use only. Only take one dose of Abseamed from each syringe discarding unwanted solution before injection.

Using the pre-filled syringe with a needle safety guard

The needle safety guard covers the needle after injection to prevent needle stick injury. This does not affect normal operation of the syringe. Depress the plunger slowly and evenly until the entire dose has been given and the plunger cannot be depressed any further. While maintaining pressure on the plunger, remove the syringe from the patient. The needle safety guard will cover the needle when releasing the plunger.

Using the pre-filled syringe without a needle safety guard

Administer the dose as per standard protocol.

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

7. MARKETING AUTHORISATION HOLDER

Medice Arzneimittel Pütter GmbH & Co. KG
Kuhloweg 37
58638 Iserlohn
Germany

8. MARKETING AUTHORISATION NUMBER(S)

Abseamed 1 000 IU/0.5 mL solution for injection in a pre-filled syringe
EU/1/07/412/001
EU/1/07/412/002
EU/1/07/412/027
EU/1/07/412/028

Abseamed 2 000 IU/1 mL solution for injection in a pre-filled syringe
EU/1/07/412/003
EU/1/07/412/004
EU/1/07/412/029
EU/1/07/412/030

Abseamed 3 000 IU/0.3 mL solution for injection in a pre-filled syringe
EU/1/07/412/005
EU/1/07/412/006
EU/1/07/412/031
EU/1/07/412/032

Abseamed 4 000 IU/0.4 mL solution for injection in a pre-filled syringe
EU/1/07/412/007
EU/1/07/412/008
EU/1/07/412/033
EU/1/07/412/034

Abseamed 5 000 IU/0.5 mL solution for injection in a pre-filled syringe
EU/1/07/412/009
EU/1/07/412/010
EU/1/07/412/035
EU/1/07/412/036

Abseamed 6 000 IU/0.6 mL solution for injection in a pre-filled syringe
EU/1/07/412/011
EU/1/07/412/012
EU/1/07/412/037
EU/1/07/412/038

Abseamed 7 000 IU/0.7 mL solution for injection in a pre-filled syringe
EU/1/07/412/017
EU/1/07/412/018
EU/1/07/412/039
EU/1/07/412/040

Abseamed 8 000 IU/0.8 mL solution for injection in a pre-filled syringe
EU/1/07/412/013
EU/1/07/412/014
EU/1/07/412/041
EU/1/07/412/042

Abseamed 9 000 IU/0.9 mL solution for injection in a pre-filled syringe
EU/1/07/412/019
EU/1/07/412/020
EU/1/07/412/043
EU/1/07/412/044

Abseamed 10 000 IU/1 mL solution for injection in a pre-filled syringe
EU/1/07/412/015
EU/1/07/412/016
EU/1/07/412/045
EU/1/07/412/046

Abseamed 20 000 IU/0.5 mL solution for injection in a pre-filled syringe
EU/1/07/412/021
EU/1/07/412/022
EU/1/07/412/047
EU/1/07/412/053
EU/1/07/412/048

Abseamed 30 000 IU/0.75 mL solution for injection in a pre-filled syringe
EU/1/07/412/023
EU/1/07/412/024
EU/1/07/412/049
EU/1/07/412/054
EU/1/07/412/050

Abseamed 40 000 IU/1 mL solution for injection in a pre-filled syringe

EU/1/07/412/025
EU/1/07/412/026
EU/1/07/412/051
EU/1/07/412/055
EU/1/07/412/052

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 August 2007
Date of latest renewal: 18 June 2012

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Novartis Pharmaceutical Manufacturing LLC
Kolodvorska cesta 27
1234 Menges
Slovenia

Name and address of the manufacturer responsible for batch release

Sandoz GmbH
Biochemiestr. 10
6250 Kundl
Austria

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Abseamed 1 000 IU/0.5 mL solution for injection in a pre-filled syringe

epoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe of 0.5 mL contains 1 000 international units (IU) corresponding to 8.4 micrograms epoetin alfa.

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, glycine, polysorbate 80, hydrochloric acid, sodium hydroxide, and water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe of 0.5 mL
6 pre-filled syringes of 0.5 mL
1 pre-filled syringe of 0.5 mL with a needle safety guard
6 pre-filled syringes of 0.5 mL with a needle safety guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous and intravenous use.
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.
Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.
Keep the pre-filled syringes in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Medice Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, 58638 Iserlohn, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/412/001
EU/1/07/412/002
EU/1/07/412/027
EU/1/07/412/028

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Abseamed 1 000 IU/0.5 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL/SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Abseamed 1 000 IU/0.5 mL injection

epoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Abseamed 2 000 IU/1 mL solution for injection in a pre-filled syringe

epoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe of 1 mL contains 2 000 international units (IU) corresponding to 16.8 micrograms epoetin alfa.

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, glycine, polysorbate 80, hydrochloric acid, sodium hydroxide, and water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe of 1 mL
6 pre-filled syringes of 1 mL
1 pre-filled syringe of 1 mL with a needle safety guard
6 pre-filled syringes of 1 mL with a needle safety guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous and intravenous use.
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.
Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.
Keep the pre-filled syringes in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Medice Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, 58638 Iserlohn, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/412/003
EU/1/07/412/004
EU/1/07/412/029
EU/1/07/412/030

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Abseamed 2 000 IU/1 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL/SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Abseamed 2 000 IU/1 mL injection

epoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Abseamed 3 000 IU/0.3 mL solution for injection in a pre-filled syringe

epoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe of 0.3 mL contains 3 000 international units (IU) corresponding to 25.2 micrograms epoetin alfa.

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, glycine, polysorbate 80, hydrochloric acid, sodium hydroxide, and water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe of 0.3 mL
6 pre-filled syringes of 0.3 mL
1 pre-filled syringe of 0.3 mL with a needle safety guard
6 pre-filled syringes of 0.3 mL with a needle safety guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous and intravenous use.
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.
Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.
Keep the pre-filled syringes in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Medice Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, 58638 Iserlohn, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/412/005
EU/1/07/412/006
EU/1/07/412/031
EU/1/07/412/032

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Abseamed 3 000 IU/0.3 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL/SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Abseamed 3 000 IU/0.3 mL injection

epoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Abseamed 4 000 IU/0.4 mL solution for injection in a pre-filled syringe

epoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe of 0.4 mL contains 4 000 international units (IU) corresponding to 33.6 micrograms epoetin alfa.

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, glycine, polysorbate 80, hydrochloric acid, sodium hydroxide, and water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe of 0.4 mL
6 pre-filled syringes of 0.4 mL
1 pre-filled syringe of 0.4 mL with a needle safety guard
6 pre-filled syringes of 0.4 mL with a needle safety guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous and intravenous use.
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.
Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.
Keep the pre-filled syringes in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Medice Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, 58638 Iserlohn, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/412/007
EU/1/07/412/008
EU/1/07/412/033
EU/1/07/412/034

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Abseamed 4 000 IU/0.4 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL/SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Abseamed 4 000 IU/0.4 mL injection

epoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Abseamed 5 000 IU/0.5 mL solution for injection in a pre-filled syringe

epoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe of 0.5 mL contains 5 000 international units (IU) corresponding to 42.0 micrograms epoetin alfa.

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, glycine, polysorbate 80, hydrochloric acid, sodium hydroxide, and water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe of 0.5 mL
6 pre-filled syringes of 0.5 mL
1 pre-filled syringe of 0.5 mL with a needle safety guard
6 pre-filled syringes of 0.5 mL with a needle safety guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous and intravenous use.
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.
Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.
Keep the pre-filled syringes in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Medice Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, 58638 Iserlohn, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/412/009
EU/1/07/412/010
EU/1/07/412/035
EU/1/07/412/036

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Abseamed 5 000 IU/0.5 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL/SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Abseamed 5 000 IU/0.5 mL injection

epoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Abseamed 6 000 IU/0.6 mL solution for injection in a pre-filled syringe

epoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe of 0.6 mL contains 6 000 international units (IU) corresponding to 50.4 micrograms epoetin alfa.

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, glycine, polysorbate 80, hydrochloric acid, sodium hydroxide, and water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe of 0.6 mL
6 pre-filled syringes of 0.6 mL
1 pre-filled syringe of 0.6 mL with a needle safety guard
6 pre-filled syringes of 0.6 mL with a needle safety guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous and intravenous use.
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.
Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.
Keep the pre-filled syringes in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Medice Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, 58638 Iserlohn, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/412/011
EU/1/07/412/012
EU/1/07/412/037
EU/1/07/412/038

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Abseamed 6 000 IU/0.6 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL/SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Abseamed 6 000 IU/0.6 mL injection

epoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Abseamed 7 000 IU/0.7 mL solution for injection in a pre-filled syringe

epoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe of 0.7 mL contains 7 000 international units (IU) corresponding to 58.8 micrograms epoetin alfa.

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, glycine, polysorbate 80, hydrochloric acid, sodium hydroxide, and water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe of 0.7 mL
6 pre-filled syringes of 0.7 mL
1 pre-filled syringe of 0.7 mL with a needle safety guard
6 pre-filled syringes of 0.7 mL with a needle safety guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous and intravenous use.
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.
Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.
Keep the pre-filled syringes in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Medice Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, 58638 Iserlohn, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/412/017
EU/1/07/412/018
EU/1/07/412/039
EU/1/07/412/040

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Abseamed 7 000 IU/0.7 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL/SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Abseamed 7 000 IU/0.7 mL injection

epoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Abseamed 8 000 IU/0.8 mL solution for injection in a pre-filled syringe

epoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe of 0.8 mL contains 8 000 international units (IU) corresponding to 67.2 micrograms epoetin alfa.

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, glycine, polysorbate 80, hydrochloric acid, sodium hydroxide, and water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe of 0.8 mL
6 pre-filled syringes of 0.8 mL
1 pre-filled syringe of 0.8 mL with a needle safety guard
6 pre-filled syringes of 0.8 mL with a needle safety guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous and intravenous use.
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.
Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.
Keep the pre-filled syringes in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Medice Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, 58638 Iserlohn, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/412/013
EU/1/07/412/014
EU/1/07/412/041
EU/1/07/412/042

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Abseamed 8 000 IU/0.8 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL/SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Abseamed 8 000 IU/0.8 mL injection

epoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Abseamed 9 000 IU/0.9 mL solution for injection in a pre-filled syringe

epoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe of 0.9 mL contains 9 000 international units (IU) corresponding to 75.6 micrograms epoetin alfa.

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, glycine, polysorbate 80, hydrochloric acid, sodium hydroxide, and water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe of 0.9 mL
6 pre-filled syringes of 0.9 mL
1 pre-filled syringe of 0.9 mL with a needle safety guard
6 pre-filled syringes of 0.9 mL with a needle safety guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous and intravenous use.
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.
Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.
Keep the pre-filled syringes in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Medice Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, 58638 Iserlohn, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/412/019
EU/1/07/412/020
EU/1/07/412/043
EU/1/07/412/044

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Abseamed 9 000 IU/0.9 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL/SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Abseamed 9 000 IU/0.9 mL injection

epoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Abseamed 10 000 IU/1 mL solution for injection in a pre-filled syringe

epoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe of 1 mL contains 10 000 international units (IU) corresponding to 84.0 micrograms epoetin alfa.

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, glycine, polysorbate 80, hydrochloric acid, sodium hydroxide, and water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe of 1 mL
6 pre-filled syringes of 1 mL
1 pre-filled syringe of 1 mL with a needle safety guard
6 pre-filled syringes of 1 mL with a needle safety guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous and intravenous use.
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.
Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.
Keep the pre-filled syringes in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Medice Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, 58638 Iserlohn, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/412/015
EU/1/07/412/016
EU/1/07/412/045
EU/1/07/412/046

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Abseamed 10 000 IU/1 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL/SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Abseamed 10 000 IU/1 mL injection

epoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Abseamed 20 000 IU/0.5 mL solution for injection in a pre-filled syringe

epoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe of 0.5 mL contains 20 000 international units (IU) corresponding to 168.0 micrograms epoetin alfa.

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, glycine, polysorbate 80, hydrochloric acid, sodium hydroxide, and water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe of 0.5 mL
6 pre-filled syringes of 0.5 mL
1 pre-filled syringe of 0.5 mL with a needle safety guard
4 pre-filled syringes of 0.5 mL with a needle safety guard
6 pre-filled syringes of 0.5 mL with a needle safety guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous and intravenous use.
Read the package leaflet before use.

Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.
Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.
Keep the pre-filled syringes in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Medice Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, 58638 Iserlohn, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/412/021
EU/1/07/412/022
EU/1/07/412/047
EU/1/07/412/053
EU/1/07/412/048

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Abseamed 20 000 IU/0.5 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL/SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Abseamed 20 000 IU/0.5 mL injection

epoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Abseamed 30 000 IU/0.75 mL solution for injection in a pre-filled syringe
epoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe of 0.75 mL contains 30 000 international units (IU) corresponding to 252.0 micrograms epoetin alfa.

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, glycine, polysorbate 80, hydrochloric acid, sodium hydroxide, and water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe of 0.75 mL
6 pre-filled syringes of 0.75 mL
1 pre-filled syringe of 0.75 mL with a needle safety guard
4 pre-filled syringes of 0.75 mL with a needle safety guard
6 pre-filled syringes of 0.75 mL with a needle safety guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous and intravenous use.
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.
Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.
Keep the pre-filled syringes in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Medice Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, 58638 Iserlohn, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/412/023
EU/1/07/412/024
EU/1/07/412/049
EU/1/07/412/054
EU/1/07/412/050

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Abseamed 30 000 IU/0.75 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL/SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Abseamed 30 000 IU/0.75 mL injection

epoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Abseamed 40 000 IU/1 mL solution for injection in a pre-filled syringe

epoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 pre-filled syringe of 1 mL contains 40 000 international units (IU) corresponding to 336.0 micrograms epoetin alfa.

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, glycine, polysorbate 80, hydrochloric acid, sodium hydroxide, and water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe of 1 mL
6 pre-filled syringes of 1 mL
1 pre-filled syringe of 1 mL with a needle safety guard
4 pre-filled syringes of 1 mL with a needle safety guard
6 pre-filled syringes of 1 mL with a needle safety guard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous and intravenous use.
Read the package leaflet before use.

Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.
Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.
Keep the pre-filled syringes in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Medice Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, 58638 Iserlohn, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/412/025
EU/1/07/412/026
EU/1/07/412/051
EU/1/07/412/055
EU/1/07/412/052

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Abseamed 40 000 IU/1 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL/SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Abseamed 40 000 IU/1 mL injection

epoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Abseamed 1 000 IU/0.5 mL solution for injection in a pre-filled syringe

Abseamed 2 000 IU/1 mL solution for injection in a pre-filled syringe

Abseamed 3 000 IU/0.3 mL solution for injection in a pre-filled syringe

Abseamed 4 000 IU/0.4 mL solution for injection in a pre-filled syringe

Abseamed 5 000 IU/0.5 mL solution for injection in a pre-filled syringe

Abseamed 6 000 IU/0.6 mL solution for injection in a pre-filled syringe

Abseamed 7 000 IU/0.7 mL solution for injection in a pre-filled syringe

Abseamed 8 000 IU/0.8 mL solution for injection in a pre-filled syringe

Abseamed 9 000 IU/0.9 mL solution for injection in a pre-filled syringe

Abseamed 10 000 IU/1 mL solution for injection in a pre-filled syringe

Abseamed 20 000 IU/0.5 mL solution for injection in a pre-filled syringe

Abseamed 30 000 IU/0.75 mL solution for injection in a pre-filled syringe

Abseamed 40 000 IU/1 mL solution for injection in a pre-filled syringe
epoetin alfa

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Abseamed is and what it is used for

Abseamed contains the active substance epoetin alfa, a protein that stimulates the bone marrow to produce more red blood cells which carry haemoglobin (a substance that transports oxygen). Epoetin alfa is a copy of the human protein erythropoietin (ee-rith-roe-po-eh-tin) and acts in the same way.

Abseamed is used to treat symptomatic anaemia caused by kidney disease:
- in children on haemodialysis
- in adults on haemodialysis or peritoneal dialysis

- in severely anaemic adults not yet undergoing dialysis

If you have kidney disease, you may be short of red blood cells if your kidney does not produce enough erythropoietin (necessary for red cell production). Abseamed is prescribed to stimulate your bone marrow to produce more red blood cells.

Abseamed is used to treat anaemia in adults receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma (bone marrow cancer) who may have a need for a blood transfusion. Abseamed can reduce the need for a blood transfusion in these patients.

Abseamed is used in moderately anaemic adults who donate some of their blood before surgery, so that it can be given back to them during or after the operation. Because Abseamed stimulates the production of red blood cells, doctors can take more blood from these people.

Abseamed is used in moderately anaemic adults about to have major orthopaedic surgery (for example hip or knee replacement operations), to reduce the potential need for blood transfusions.

Abseamed is used to treat anaemia in adults with a bone marrow disorder that causes a severe disruption in the creation of blood cells (myelodysplastic syndromes). Abseamed can reduce the need for a blood transfusion.

2. What you need to know before you use Abseamed

Do not use Abseamed

- **if you are allergic** to epoetin alfa or any of the other ingredients of this medicine (listed in section 6).
- **if you have been diagnosed with Pure Red Cell Aplasia** (the bone marrow cannot produce enough red blood cells) after previous treatment with any product that stimulates red blood cell production (including Abseamed). See section 4.
- **if you have high blood pressure** not properly controlled with medicines.
- to stimulate the production of your red blood cells (so that doctors can take more blood from you) **if you cannot have transfusions with your own blood** during or after surgery.
- **if you are due to have major elective orthopaedic surgery** (such as hip or knee surgery), and you:
  - have severe heart disease
  - have severe disorders of the veins and arteries
  - have recently had a heart attack or stroke
  - can't take medicines to thin the blood

  Abseamed may not be suitable for you. Please discuss with your doctor. While on Abseamed, some people need medicines to reduce the risk of blood clots. **If you can't take medicines that prevent blood clotting, you must not have Abseamed.**

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Abseamed.

Abseamed and other products that stimulate red cell production may increase the risk of developing blood clots in all patients. This risk may be higher if you have other risk factors for developing blood clots *(for example, if you have had a blood clot in the past or are overweight, have diabetes, have heart disease or you are off your feet for a long time because of surgery or illness).* Please tell your doctor about any of these things. Your doctor will help you to decide if Abseamed is suitable for you.

It is important to tell your doctor if any of the following apply to you**.** You may still be able to use Abseamed, but discuss it with your doctor first.

If you know you suffer, or have suffered, from:
- **high blood pressure;**
- **epileptic seizures or fits**;
- **liver disease;**
- **anaemia from other causes;**
- **porphyria (a rare blood disorder).**

If you are a patient with chronic renal failure, and particularly if you do not respond properly to Abseamed, your doctor will check your dose of Abseamed because repeatedly increasing your dose of Abseamed if you are not responding to treatment may increase the risk of having a problem of the heart or the blood vessels and could increase risk of myocardial infarction, stroke and death.

If you are a cancer patient be aware that products that stimulate red blood cell production (like Abseamed) may act as a growth factor and therefore in theory may affect the progression of your cancer.
Depending on your individual situation a blood transfusion may be preferable. Please discuss this with your doctor.

If you are a cancer patient, be aware that use of Abseamed may be associated with shorter survival and a higher death rate in head and neck, and metastatic breast cancer patients who are receiving chemotherapy.

Serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with epoetin treatment.

SJS/TEN can appear initially as reddish target-like spots or circular patches often with central blisters on the trunk. Also, ulcers of mouth, throat, nose, genitals and eyes (red and swollen eyes) can occur. These serious skin rashes are often preceded by fever and/or flu-like symptoms. The rashes may progress to widespread peeling of the skin and life-threatening complications.

If you develop a serious rash or another of these skin symptoms, stop taking Abseamed and contact your doctor or seek medical attention immediately.

Take special care with other products that stimulate red blood cell production:

Abseamed is one of a group of products that stimulate the production of red blood cells like the human protein erythropoietin does. Your healthcare professional will always record the exact product you are using. If you are given a product in this group other than Abseamed during your treatment, speak to your doctor or pharmacist before using it.

Other medicines and Abseamed

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

If you are a patient with hepatitis C and you receive interferon and ribavirin

You should discuss this with your doctor because a combination of epoetin alfa with interferon and ribavirin has led to a loss of effect and development of a condition called pure red cell aplasia (PRCA), a severe form of anaemia, in rare cases. Binocrit is not approved in the management of anaemia associated with hepatitis C.

If you are taking a medicine called cyclosporin (used e.g. after kidney transplants), your doctor may order blood tests to check the level of cyclosporin while you are taking Abseamed.

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

If you visit a hospital, clinic or family doctor, tell them you are having Abseamed treatment. It may affect other treatments or test results.

Pregnancy, breast-feeding and fertility

It is important to tell your doctor if any of the following apply to you. You may still be able to use Abseamed, but discuss it with your doctor first:

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

No data on the effects of Abseamed on fertility are available

Abseamed contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

3. How to use Abseamed

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Your doctor has carried out blood tests and decided you need Abseamed.

Abseamed may be given by injection:

- **Either** into a vein or a tube that goes into a vein (intravenously)
- **Or** under the skin (subcutaneously).

Your doctor will decide how Abseamed will be injected. Usually the injections will be given to you by a doctor, nurse or other health care professional. Some people, depending on why they need Abseamed treatment, may later learn how to inject themselves under the skin: see *Instructions on how to inject Abseamed yourself* at the end of the leaflet.

Abseamed should not be used:

- after the expiry date on the label and outer carton
- if you know, or think that it may have been accidentally frozen, or
- if there has been a refrigerator failure.

The dose of Abseamed you receive is based on your body weight in kilograms. The cause of your anaemia is also a factor in your doctor deciding the correct dose.

Your doctor will monitor your blood pressure regularly while you are using Abseamed.

People with kidney disease

- Your doctor will maintain your haemoglobin level between 10 and 12 g/dL as a high haemoglobin level may increase the risk of blood clots and death. In children the haemoglobin level should be maintained between 9.5 and 11 g/dL.
- **The usual starting dose** of Abseamed for adults and children is 50 International Units (IU) per kilogram (/kg) of body weight given three times a week. For patients on peritoneal dialysis Abseamed may be given twice a week.

- For adults and children Abseamed is given as an injection either into a vein (intravenously) or a tube that goes into a vein. When this access (via a vein or tube) is not readily available, your doctor may decide that Abseamed should be injected under the skin (subcutaneously). This includes patients on dialysis and patients not yet on dialysis.
- Your doctor will order regular blood tests to see how your anaemia is responding and may adjust the dose, usually no more frequently than every four weeks. A rise in haemoglobin of greater than 2 g/dL over a four week period should be avoided.
- Once your anaemia has been corrected, your doctor will continue to check your blood regularly. Your Abseamed dose and frequency of administration may be further adjusted to maintain your response to treatment. Your doctor will use the lowest effective dose to control the symptoms of your anaemia.
- If you do not respond adequately to Abseamed, your doctor will check your dose and will inform you if you need to change doses of Abseamed.
- If you are on a more extended dosing interval (greater than once weekly) of Abseamed, you may not maintain adequate haemoglobin levels and you may require an increase in Abseamed dose or frequency of administration.
- You may be given iron supplements before and during Abseamed treatment to make it more effective.
- If you are having dialysis treatment when you begin treatment with Abseamed, your dialysis regime may need to be adjusted. Your doctor will decide this.

Adults on chemotherapy

- Your doctor may initiate treatment with Abseamed if your haemoglobin is 10 g/dL or less.
- Your doctor will maintain your haemoglobin level between 10 and 12 g/dL as a high haemoglobin level may increase the risk of blood clots and death.
- The starting dose is **either** 150 IU per kilogram body weight three times a week **or** 450 IU per kilogram body weight once a week.
- Abseamed is given by injection under the skin.
- Your doctor will order blood tests, and may adjust the dose, depending on how your anaemia responds to Abseamed treatment.
- You may be given iron supplements before and during Abseamed treatment to make it more effective.
- You will usually continue Abseamed treatment for one month after the end of chemotherapy.

Adults donating their own blood

- **The usual dose** is 600 IU per kilogram body weight twice a week.
- Abseamed is given by injection into a vein immediately after you have donated blood for 3 weeks before your surgery.
- You may be given iron supplements before and during Abseamed treatment to make it more effective.

Adults scheduled for major orthopaedic surgery

- **The recommended dose** is 600 IU per kilogram body weight once a week.
- Abseamed is given by injection under the skin each week for three weeks before surgery and on the day of surgery.
- If there is a medical need to reduce the time before your operation, you will be given a daily dose of 300 IU/kg for up to ten days before surgery, on the day of surgery and for four days immediately afterwards.
- If blood tests show your haemoglobin is too high before the operation, the treatment will be stopped.
- You may be given iron supplements before and during Abseamed treatment to make it more effective.

Adults with myelodysplastic syndrome

- Your doctor may initiate treatment with Abseamed if your haemoglobin is 10 g/dL or less. The aim of treatment is to maintain your haemoglobin level between 10 and 12 g/dL as a higher haemoglobin level may increase the risk of blood clots and death.
- Abseamed is given by injection under the skin.
- The starting dose is 450 IU per kilogram bodyweight once a week.
- Your doctor will order blood tests, and may adjust the dose, depending on how your anaemia responds to Abseamed treatment.

Instructions on how to inject Abseamed yourself

When treatment starts, Abseamed is usually injected by a medical professional or a nurse. Later, your doctor may suggest that you or your caregiver learn how to inject Abseamed under the skin (*subcutaneously*) yourself.

- **Do not attempt to inject yourself unless you have been trained to do so by your doctor or nurse.**
- **Always use Abseamed exactly as instructed by your doctor or nurse.**
- **Ensure that you only inject the amount of liquid as instructed by your doctor or nurse.**
- **Only use Abseamed if it has been stored correctly – see section 5*, How to store Abseamed.***
- **Before use, leave the Abseamed syringe to stand until it reaches room temperature. This usually takes between 15 and 30 minutes. Use the syringe within 3 days of taking it out of the refrigerator.**

Only take one dose of Abseamed from each syringe.

If Abseamed is injected under the skin (subcutaneously), the amount injected is not normally more than one millilitre (1 mL) in a single injection.

Abseamed is given alone and not mixed with other liquids for injection.

Do not shake Abseamed syringes. Prolonged vigorous shaking may damage the product. If the product has been shaken vigorously, don't use it.

Instructions on how to inject yourself with Abseamed can be found at the end of this leaflet.

If you use more Abseamed than you should

Tell your doctor or nurse immediately if you think too much Abseamed has been injected. Side effects from an overdose of Abseamed are unlikely.

If you forget to use Abseamed

Make the next injection as soon as you remember. If you are within a day of your next injection, forget the missed one and carry on with your normal schedule. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor, nurse or pharmacist.

4. Possible side effects

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

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

Serious skin rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in association with epoetin treatment. These can appear as reddish target-like macules or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes and can be preceded by fever and flu-like symptoms. Stop using Abseamed if you develop these symptoms and contact your doctor or seek medical attention immediately. See also section 2.

Very common side effects
These may affect more than 1 in 10 people.
- **Diarrhoea**
- **Feeling sick in your stomach**
- **Vomiting**
- **Fever**
- **Respiratory tract congestion**, such as stuffy nose and sore throat, has been reported in patients with kidney disease not yet on dialysis.

Common side effects
These may affect up to 1 in 10 people.

- **Increased blood pressure**. **Headaches**, particularly sudden, stabbing migraine-like headaches, **feeling confused or having fits** may be signs of a sudden increase in blood pressure. This requires urgent treatment. Raised blood pressure may require treatment with medicines (or adjustment to any medicines you already take for high blood pressure).
- **Blood clots** (including deep vein thrombosis and embolism) that may require urgent treatment. You may have **chest pain, breathlessness, and painful swelling and redness, usually in the leg** as symptoms.
- **Cough.**
- **Skin rashes, which may result from an allergic reaction.**
- **Bone or muscle pain.**
- **Flu-like symptoms**, such as headache, aches and pains in the joints, feeling of weakness, chills, tiredness and dizziness. These may be more common at the start of treatment. If you have these symptoms during injection into the vein, a slower delivery of the injection may help to avoid them in the future.
- **Redness, burning and pain at the site of injection.**
- **Swelling of the ankles, feet or fingers.**
- **Arm or leg pain.**

Uncommon side effects
These may affect up to 1 in 100 people.

- **High levels of blood potassium** which can cause abnormal heart rhythm (this is a very common side effect in patients on dialysis).
- **Fits.**
- **Nose or airway congestion.**
- **Allergic reaction.**
- **Hives.**

Rare side effects
These may affect up to 1 in 1,000 people.

- **Symptoms of pure red cell aplasia (PRCA)**

PRCA means the bone marrow does not make enough red blood cells. PRCA causes **sudden and severe anaemia. The symptoms are:**
- **unusual tiredness,**
- **feeling dizzy,**

- **breathlessness.**

PRCA has been very rarely reported mostly in patients with kidney disease after months to years of treatment with epoetin alfa and other products that stimulate red blood cell production.

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

- Severe allergic reaction that may include:
  - a swollen face, lips, mouth, tongue or throat,
  - difficulty swallowing or breathing,
  - itchy rash (hives).

- Problem with the blood that may cause pain, dark coloured urine or increased sensitivity of the skin to sunlight (porphyria).

If you are receiving haemodialysis:

- **Blood clots** (thrombosis) may form in your dialysis shunt. This is more likely if you have low blood pressure or if your fistula has complications.

- **Blood clots** may also form in your haemodialysis system. Your doctor may decide to increase your heparin dose during dialysis.

Tell your doctor or nurse immediately if you are aware of any of these effects, or if you notice any other effects while you are receiving treatment with Abseamed**.**

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Abseamed

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.
- Store and transport refrigerated (2 °C-8 °C).
- You may take Abseamed out of the refrigerator and keep it at room temperature (up to 25 °C) for no longer than 3 days. Once a syringe has been removed from the refrigerator and has reached room temperature (up to 25 °C) it must either be used within 3 days or disposed of.
- Do not freeze or shake.
- Store in the original package in order to protect from light.

Do not use this medicine if you notice that
- it may have been accidentally frozen, or
- if there has been a refrigerator failure,
- the liquid is coloured or you can see particles floating in it,
- the seal is broken.

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

6. Contents of the pack and other information

What Abseamed contains

- **The active substance is**: epoetin alfa (for quantity see the table below).
- **The other ingredients are: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, glycine, polysorbate 80, hydrochloric acid (for pH-adjustment), sodium hydroxide (for pH-adjustment), and water for injections.**

What Abseamed looks like and contents of the pack

Abseamed is presented as a clear, colourless solution for injection in a pre-filled syringe. The syringes are sealed in a blister.

Presentation	**Corresponding Presentations in Quantity/Volume for each Strength**	**Amount of epoetin alfa**
Pre-filled syringes*	2 000 IU/mL:	
	1 000 IU/0.5 mL	8.4 micrograms
	2 000 IU/1 mL	16.8 micrograms
	10 000 IU/mL:	
	3 000 IU/0.3 mL	25.2 micrograms
	4 000 IU/0.4 mL	33.6 micrograms
	5 000 IU/0.5 mL	42.0 micrograms
	6 000 IU/0.6 mL	50.4 micrograms
	7 000 IU/0.7 mL	58.8 micrograms
	8 000 IU/0.8 mL	67.2 micrograms
	9 000 IU/0.9 mL	75.6 micrograms
	10 000 IU/1 mL	84.0 micrograms
	40 000 IU/mL:	
	20 000 IU/0.5 mL	168.0 micrograms
	30 000 IU/0.75 mL	252.0 micrograms
	40 000 IU/1 mL	336.0 micrograms

*Pack size of 1, 4 or 6 pre-filled syringe(s) with or without a needle safety guard.
Not all pack sizes may be marketed.

Marketing Authorisation Holder

Medice Arzneimittel Pütter GmbH & Co. KG
Kuhloweg 37
58638 Iserlohn
Germany

Manufacturer

Sandoz GmbH
Biochemiestr. 10
6250 Kundl
Austria

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

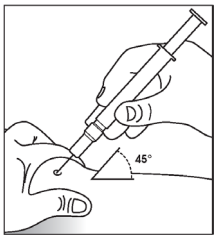
Instructions on how to inject yourself (for patients with symptomatic anaemia caused by kidney disease, for adult patients receiving chemotherapy, adult patients scheduled for orthopaedic surgery, or adult patients with myelodysplastic syndromes only)

This section contains information on how to give yourself an injection of Abseamed. **It is important that you do not try to give yourself the injection unless you have received special training from your doctor or nurse.** Abseamed is provided with or without a needle safety guard and you will be shown how to use this by your doctor or nurse. If you are not sure about giving the injection or you have any questions, please ask your doctor or nurse for help.

WARNING: Do not use if the syringe has been dropped onto a hard surface or dropped after removing the needle cap. Do not use the Abseamed prefilled syringe if it is broken. Return the prefilled syringe and the package it came in to the pharmacy.

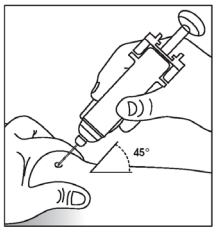
1. Wash your hands.
2. Remove one syringe from the pack and remove the protective cap from the injection needle. Syringes are embossed with graduation rings in order to enable partial use if required. Each graduation ring corresponds to a volume of 0.1 mL. If partial use of a syringe is required, remove unwanted solution before injection.
3. Clean the skin at the injection site using an alcohol wipe.
4. Form a skin fold by pinching the skin between thumb and forefinger.
5. Insert the needle into the skin fold with a quick, firm action. Inject the Abseamed solution as you have been shown by your doctor. You should check with your doctor or pharmacist if you are not sure.

<u>Pre-filled syringe without needle safety guard</u>



6. Always keeping your skin pinched, depress the plunger slowly and evenly.
7. After injecting the liquid, remove the needle and let go of your skin. Apply pressure over the injection site with a dry, sterile pad.
8. Discard any unused product or waste material. Only use each syringe for one injection.

<u>Pre-filled syringe with needle safety guard</u>



6. Always keeping your skin pinched, depress the plunger slowly and evenly until the entire dose has been given and the plunger cannot be depressed any further. Do not release the pressure on the plunger!
7. After injecting the liquid, remove the needle while maintaining pressure on the plunger and then let go of your skin. Apply pressure over the injection site with a dry, sterile pad.
8. Let go of the plunger. The needle safety guard will rapidly move to cover the needle.
9. Discard any unused product or waste material. Only use each syringe for one injection.