SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Aranesp 10 micrograms solution for injection in pre-filled syringe.
Aranesp 20 micrograms solution for injection in pre-filled syringe.
Aranesp 30 micrograms solution for injection in pre-filled syringe.
Aranesp 40 micrograms solution for injection in pre-filled syringe.
Aranesp 50 micrograms solution for injection in pre-filled syringe.
Aranesp 60 micrograms solution for injection in pre-filled syringe.
Aranesp 80 micrograms solution for injection in pre-filled syringe.
Aranesp 100 micrograms solution for injection in pre-filled syringe.
Aranesp 130 micrograms solution for injection in pre-filled syringe.
Aranesp 150 micrograms solution for injection in pre-filled syringe.
Aranesp 300 micrograms solution for injection in pre-filled syringe.
Aranesp 500 micrograms solution for injection in pre-filled syringe.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Aranesp 10 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 10 micrograms of darbepoetin alfa in 0.4 mL (25 mcg/mL).
Aranesp 20 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 20 micrograms of darbepoetin alfa in 0.5 mL (40 mcg/mL).
Aranesp 30 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 30 micrograms of darbepoetin alfa in 0.3 mL (100 mcg/mL).
Aranesp 40 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 40 micrograms of darbepoetin alfa in 0.4 mL (100 mcg/mL).
Aranesp 50 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 50 micrograms of darbepoetin alfa in 0.5 mL (100 mcg/mL).
Aranesp 60 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 60 micrograms of darbepoetin alfa in 0.3 mL (200 mcg/mL).
Aranesp 80 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 80 micrograms of darbepoetin alfa in 0.4 mL (200 mcg/mL).
Aranesp 100 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 100 micrograms of darbepoetin alfa in 0.5 mL (200 mcg/mL).
Aranesp 130 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 130 micrograms of darbepoetin alfa in 0.65 mL (200 mcg/mL).
Aranesp 150 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 150 micrograms of darbepoetin alfa in 0.3 mL (500 mcg/mL).
Aranesp 300 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 300 micrograms of darbepoetin alfa in 0.6 mL (500 mcg/mL).
Aranesp 500 micrograms solution for injection in pre-filled syringe
Each pre-filled syringe contains 500 micrograms of darbepoetin alfa in 1 mL (500 mcg/mL).

Darbepoetin alfa is produced by gene-technology in Chinese Hamster Ovary Cells (CHO-K1).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection) in pre-filled syringe.

Clear, colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adults and paediatric patients (see section 4.2).

Treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

4.2 Posology and method of administration

Aranesp treatment should be initiated by physicians experienced in the above mentioned indications.

Posology

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

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. Aranesp should be administered either subcutaneously or intravenously in order to increase haemoglobin to not greater than 12 g/dL (7.5 mmol/L). Subcutaneous use is preferable in patients who are not receiving haemodialysis to avoid the puncture of peripheral veins.

Patients should be monitored closely to ensure that the lowest approved effective dose of Aranesp is used to provide adequate control 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 Aranesp doses in patients with chronic renal failure. In patients with a poor haemoglobin response to Aranesp, alternative explanations for the poor response should be considered (see sections 4.4 and 5.1).

Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10 g/dL (6.2 mmol/L) to 12 g/dL (7.5 mmol/L). A sustained haemoglobin level of greater than 12 g/dL (7.5 mmol/L) should be avoided; guidance for appropriate dose adjustment for

when haemoglobin values exceeding 12 g/dL (7.5 mmol/L) are observed are described below. 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.

Treatment with Aranesp is divided into two stages, correction and maintenance phase. Guidance is given separately for adult and paediatric patients.

Adult patients with chronic renal failure

Correction phase:

The initial dose by subcutaneous or intravenous administration is 0.45 mcg/kg body weight, as a single injection once weekly. Alternatively, in patients not on dialysis, the following initial doses can also be administered subcutaneously as a single injection: 0.75 mcg/kg once every two weeks or 1.5 mcg/kg once monthly. If the increase in haemoglobin is inadequate (less than 1 g/dL (0.6 mmol/L) in four weeks) increase the dose by approximately 25%. Dose increases must not be made more frequently than once every four weeks.

If the rise in haemoglobin is greater than 2 g/dL (1.25 mmol/L) in four weeks reduce the dose by approximately 25%. If the haemoglobin exceeds 12 g/dL (7.5 mmol/L), a dose reduction should be considered. If the haemoglobin continues to increase, the dose should be reduced by approximately 25%. If after a dose reduction, haemoglobin continues to increase, the dose should be temporarily withheld until the haemoglobin begins to decrease, at which point therapy should be reinitiated at approximately 25% lower than the previous dose.

The haemoglobin should be measured every one or two weeks until it is stable. Thereafter the haemoglobin can be measured at longer intervals.

Maintenance phase:

In dialysis patients, Aranesp may continue to be administered as a single injection once weekly or once every two weeks. Dialysis patients converting from once weekly to once every other week dosing with Aranesp should initially receive a dose equivalent to twice the previous once weekly dose.

In patients not on dialysis, Aranesp may continue to be administered as a single injection once weekly or once every two weeks or once monthly. For patients treated with Aranesp once every two weeks, after the target haemoglobin has been achieved, Aranesp may then be administered subcutaneously once monthly using an initial dose equal to twice the previous once every two week dose.

Dosing should be titrated as necessary to maintain the haemoglobin target.

If a dose adjustment is required to maintain haemoglobin at the desired level, it is recommended that the dose is adjusted by approximately 25%.

If the rise in haemoglobin is greater than 2 g/dL (1.25 mmol/L) in four weeks reduce the dose by approximately 25%, depending on the rate of increase. If the haemoglobin exceeds 12 g/dL (7.5 mmol/L), a dose reduction should be considered. If the haemoglobin continues to increase, the dose should be reduced by approximately 25%. If after a dose reduction, haemoglobin continues to increase, the dose should be temporarily withheld until the haemoglobin begins to decrease, at which point therapy should be reinitiated at approximately 25% lower than the previous dose.

After any dose or schedule adjustment the haemoglobin should be monitored every one or two weeks. Dose changes in the maintenance phase of treatment should not be made more frequently than every two weeks.

When changing the route of administration the same dose must be used and the haemoglobin monitored every one or two weeks so that the appropriate dose adjustments can be made to keep the haemoglobin at the desired level.

Clinical studies have demonstrated that adult patients receiving r-HuEPO one, two or three times weekly may be converted to once weekly or once every other week Aranesp. The initial weekly dose of Aranesp (mcg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 200. The initial every other week dose of Aranesp (mcg/every other week) can be determined by dividing the total cumulative dose of r-HuEPO administered over a two-week period by 200. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Aranesp for r-HuEPO the haemoglobin should be monitored every one or two weeks and the same route of administration should be used.

Paediatric population with chronic renal failure

Treatment of paediatric patients younger than 1 year of age has not been studied in randomised clinical trials (see section 5.1).

Correction phase:

For patients ≥ 1 year of age, the initial dose by subcutaneous or intravenous administration is 0.45 mcg/kg body weight, as a single injection once weekly. Alternatively, in patients not on dialysis, an initial dose of 0.75 mcg/kg may be administered subcutaneously as a single injection once every two weeks. If the increase in haemoglobin is inadequate (less than 1 g/dL (0.6 mmol/L) in four weeks) increase the dose by approximately 25%. Dose increases must not be made more frequently than once every four weeks.

If the rise in haemoglobin is greater than 2 g/dL (1.25 mmol/L) in four weeks reduce the dose by approximately 25%, depending on the rate of increase. If the haemoglobin exceeds 12 g/dL (7.5 mmol/L), a dose reduction should be considered. If the haemoglobin continues to increase, the dose should be reduced by approximately 25%. If after a dose reduction, haemoglobin continues to increase, the dose should be temporarily withheld until the haemoglobin begins to decrease, at which point therapy should be reinitiated at approximately 25% lower than the previous dose.

The haemoglobin should be measured every one or two weeks until it is stable. Thereafter the haemoglobin can be measured at longer intervals.

Correction of anaemia in paediatric patients with once monthly Aranesp dosing frequency has not been studied.

Maintenance phase:

For paediatric patients ≥ 1 year of age, in the maintenance phase, Aranesp may continue to be administered as a single injection once weekly or once every two weeks. Patients < 6 years of age may need higher doses for maintenance of haemoglobin than patients above that age. Dialysis patients converting from once weekly to once every other week dosing with Aranesp should initially receive a dose equivalent to twice the previous once weekly dose.

In patients ≥ 11 years of age not on dialysis, once the target haemoglobin has been achieved with once every two week dosing, Aranesp may be administered subcutaneously once monthly using an initial dose equal to twice the previous once every two week dose.

Clinical data in paediatric patients has demonstrated that patients receiving r-HuEPO two or three times weekly may be converted to once weekly Aranesp, and those receiving r-HuEPO once weekly may be converted to once every other week Aranesp. The initial weekly paediatric dose of Aranesp (mcg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. The initial every other week dose of Aranesp (mcg/every other week) can be determined by dividing the total cumulative dose of r-HuEPO administered over a two-week period by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Aranesp for r-HuEPO the haemoglobin should be monitored every one or two weeks and the same route of administration should be used.

Dosing should be titrated as necessary to maintain the haemoglobin target.

If a dose adjustment is required to maintain haemoglobin at the desired level, it is recommended that the dose is adjusted by approximately 25%.

If the rise in haemoglobin is greater than 2 g/dL (1.25 mmol/L) in four weeks reduce the dose by approximately 25%, depending on the rate of increase. If the haemoglobin exceeds 12 g/dL (7.5 mmol/L), a dose reduction should be considered. If the haemoglobin continues to increase, the dose should be reduced by approximately 25%. If after a dose reduction, haemoglobin continues to increase, the dose should be temporarily withheld until the haemoglobin begins to decrease, at which point therapy should be reinitiated at approximately 25% lower than the previous dose.

Patients starting dialysis during treatment with Aranesp should be closely monitored for adequate control of their haemoglobin.

After any dose or schedule adjustment the haemoglobin should be monitored every one or two weeks. Dose changes in the maintenance phase of treatment should not be made more frequently than every two weeks.

When changing the route of administration the same dose must be used and the haemoglobin monitored every one or two weeks so that the appropriate dose adjustments can be made to keep the haemoglobin at the desired level.

Treatment of symptomatic chemotherapy-induced anaemia in cancer patients

Aranesp should be administered by the subcutaneous route to patients with anaemia (e.g. haemoglobin concentration ≤ 10 g/dL (6.2 mmol/L)) in order to increase haemoglobin to not greater than 12 g/dL (7.5 mmol/L). Anaemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary.

Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10 g/dL (6.2 mmol/L) to 12 g/dL (7.5 mmol/L). A sustained haemoglobin level of greater than 12 g/dL (7.5 mmol/L) should be avoided; guidance for appropriate dose adjustments for when haemoglobin values exceeding 12 g/dL (7.5 mmol/L) are observed are described below.

The recommended initial dose is 500 mcg (6.75 mcg/kg) given once every three weeks, or once weekly dosing can be given at 2.25 mcg/kg body weight. If the clinical response of the patient (fatigue, haemoglobin response) is inadequate after nine weeks, further therapy may not be effective.

Aranesp therapy should be discontinued approximately four weeks after the end of chemotherapy.

Once the therapeutic objective for an individual patient has been achieved, the dose should be reduced by 25 to 50% in order to ensure that the lowest approved dose of Aranesp is used to maintain haemoglobin at a level that controls the symptoms of anaemia. Appropriate dose titration between 500 mcg, 300 mcg, and 150 mcg should be considered.

Patients should be monitored closely, if the haemoglobin exceeds 12 g/dL (7.5 mmol/L), the dose should be reduced by approximately 25 to 50%. Treatment with Aranesp should be temporarily discontinued if haemoglobin levels exceed 13 g/dL (8.1 mmol/L). Therapy should be reinitiated at approximately 25% lower than the previous dose after haemoglobin levels fall to 12 g/dL (7.5 mmol/L) or below.

If the rise in haemoglobin is greater than 2 g/dL (1.25 mmol/L) in 4 weeks, the dose should be reduced by 25 to 50%.

Method of administration

Aranesp may be administered subcutaneously by the patient or a carer after being trained by a doctor, nurse or pharmacist.

Aranesp 10, 20, 30, 40, 50, 60, 80, 100, 130, 150, 300, 500 micrograms solution for injection in pre-filled syringe
Aranesp is administered either subcutaneously or intravenously as described in the posology. Rotate the injection sites and inject slowly to avoid discomfort at the site of injection. Aranesp is supplied ready for use in a pre-filled syringe.

The instructions for use, handling and disposal are given in section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

The warnings and precautions information presented below includes both prefilled pen and prefilled syringe safety data.

General

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

Blood pressure should be monitored in all patients, particularly during initiation of Aranesp therapy. If blood pressure is difficult to control by initiation of appropriate measures, the haemoglobin may be reduced by decreasing or withholding the dose of Aranesp (see section 4.2). Cases of severe hypertension, including hypertensive crisis, hypertensive encephalopathy, and seizures, have been observed in CRF patients treated with Aranesp.

In order to ensure effective erythropoiesis, iron status should be evaluated for all patients prior to and during treatment and supplementary iron therapy may be necessary.

Non-response to therapy with Aranesp should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of ESAs and should therefore be corrected. Intercurrent infections, inflammatory or traumatic episodes, occult blood loss, haemolysis, severe aluminium toxicity, underlying haematologic diseases, or bone marrow fibrosis may also compromise the erythropoietic response. A reticulocyte count should be considered as part of the evaluation. If typical causes of non-response are excluded, and the patient has reticulocytopenia, an examination of the bone marrow should be considered. If the bone marrow is consistent with PRCA, testing for anti-erythropoietin antibodies should be performed.

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

Pure red cell aplasia caused by neutralising anti-erythropoietin antibodies has been reported in association with ESAs, including Aranesp. This has been predominantly reported in patients with CRF treated subcutaneously. These antibodies have been shown to cross-react with all erythropoietic proteins, and patients suspected or confirmed to have neutralising antibodies to erythropoietin should not be switched to Aranesp (see section 4.8).

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

Active liver disease was an exclusion criteria in all studies of Aranesp, therefore no data are available from patients with impaired liver function. Since the liver is thought to be the principal route of elimination of darbepoetin alfa and r-HuEPO, Aranesp should be used with caution in patients with liver disease.

Aranesp should also be used with caution in those patients with sickle cell anaemia.

Misuse of Aranesp by healthy persons may lead to an excessive increase in packed cell volume. This may be associated with life-threatening complications of the cardiovascular system.

The needle cap of the pre-filled syringe or pre-filled pen contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

Aranesp should be used with caution in patients with epilepsy. Convulsions have been reported in patients receiving Aranesp.

The reported risk of thrombotic vascular events (TVEs) should be carefully weighed against the benefits to be derived from treatment with darbepoetin 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).

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

Chronic renal failure patients

In patients with chronic renal failure, maintenance haemoglobin concentration should not exceed the upper limit of the target haemoglobin concentration recommended in section 4.2. In clinical studies, an increased risk of death, serious cardiovascular or cerebrovascular events including stroke, and vascular access thrombosis was observed when ESAs were administered to target a haemoglobin of greater than 12 g/dL (7.5 mmol/L).

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

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

Supplementary iron therapy is recommended for all patients with serum ferritin values below 100 mcg/L or whose transferrin saturation is below 20%.

Serum potassium levels should be monitored regularly during Aranesp therapy. Potassium elevation has been reported in a few patients receiving Aranesp, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Aranesp administration until the level has been corrected.

Cancer patients

Effect on tumour growth

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

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

- shortened time to tumour progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a haemoglobin of greater than 14 g/dL (8.7 mmol/L), ESAs are not indicated for use in this patient population.

- shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a haemoglobin of 12-14 g/dL (7.5-8.7 mmol/L).

- increased risk of death when administered to target a haemoglobin of 12 g/dL (7.5 mmol/L) in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for use in this patient population.

- an observed 9% increase in risk for PD or death in the epoetin alfa plus SOC 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).

- non-inferiority of darbepoetin alfa to placebo for overall survival and progression free survival in patients with advanced stage non-small cell lung cancer receiving chemotherapy when administered to a target haemoglobin of 12 g/dL (7.5 mmol/L) (see section 5.1).

In view of the above, in some clinical situations blood transfusion should be the preferred treatment for the management of anaemia in patients with cancer. The decision to administer recombinant erythropoietins should be based on a benefit-risk assessment with the participation of the individual patient, which should take into account the specific clinical context. Factors that should be considered in this assessment should include the type of tumour and its stage; the degree of anaemia; life-expectancy; the environment in which the patient is being treated; and patient preference (see section 5.1).

In patients with solid tumours or lymphoproliferative malignancies, if the haemoglobin value exceeds 12 g/dL (7.5 mmol/L), the dosage adaptation described in section 4.2 should be closely respected, in order to minimise the potential risk of thromboembolic events. Platelet counts and haemoglobin level should also be monitored at regular intervals.

4.5 Interaction with other medicinal products and other forms of interaction

The clinical results obtained so far do not indicate any interaction of darbepoetin alfa with other substances. However, there is potential for an interaction with substances that are highly bound to red blood cells e.g. cyclosporin, tacrolimus. If Aranesp is given concomitantly with any of these treatments, blood levels of these substances should be monitored and the dosage adjusted as the haemoglobin rises.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies with Aranesp in pregnant women.

Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. No alteration of fertility was detected.

Caution should be exercised when prescribing Aranesp to pregnant women.

Breast-feeding

It is unknown whether Aranesp is excreted in human milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Aranesp therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The warnings and precautions information presented below includes both prefilled pen and prefilled syringe safety data.

Summary of the safety profile

Identified adverse reactions associated with Aranesp are hypertension, stroke, thromboembolic events, convulsions, allergic reactions, rash/erythema and pure red cell aplasia (PRCA); see section 4.4.

Injection site pain was reported as attributable to treatment in studies where Aranesp was administered via subcutaneous injection. The injection site discomfort was generally mild and transient in nature and occurred predominantly after the first injection.

Tabulated list of adverse reactions

Incidence of adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Data are presented separately for CRF and cancer patients reflecting the different adverse reaction profile in these populations.

Chronic renal failure patients

Data presented from controlled studies included 1,357 patients, 766 who received Aranesp and 591 patients who received r-HuEPO. In the Aranesp group, 83% were receiving dialysis and 17% were not receiving dialysis. Stroke was identified as an adverse reaction in an additional clinical study (TREAT, see section 5.1).

Incidence of adverse reactions from controlled clinical studies and post-marketing experience are:

MedDRA system organ class	**Subject incidence**	**Adverse reaction**
Blood and lymphatic system disorders	Not known[2]	Pure red cell aplasia
Immune system disorders	Very common	Hypersensitivity[a]
Nervous system disorders	Common	Stroke[b]
	Uncommon[1]	Convulsions
Cardiac disorders	Very common	Hypertension
Vascular disorders	Uncommon	Thromboembolic events[c]
	Uncommon[1]	Dialysis vascular access thrombosis[d]
Skin and subcutaneous tissue disorders	Common	Rash/erythema[e]
	Not known[2]	SJS/TEN, erythema multiforme, blistering, skin exfoliation
General disorders and administration site conditions	Common	Injection site pain
	Uncommon[1]	Injection site bruising Injection site haemorrhage

Source: Includes 5 randomised, double-blind, active-controlled studies (970200, 970235, 980117, 980202, and 980211) except for the adverse reaction of stroke which was identified as an adverse reaction in the TREAT study (study 20010184).

[1] Adverse reactions identified in the post-marketing environment. Per the Guideline on Summary of Product Characteristics (Revision 2, September 2009), frequency of adverse reactions identified in the post-marketing setting was determined using the "Rule of three".

[2] Frequency cannot be estimated from the available data.

[a] Hypersensitivity events includes all events under the hypersensitivity SMQ.

[b] Stroke events includes PT haemorrhagic stroke, ischaemic stroke, cerebrovascular accident, and stroke in evolution.

[c] Thromboembolic events adverse reaction includes PT embolism arterial, thrombophlebitis, thrombosis, venous thrombosis limb.

[d] Dialysis vascular access thrombosis includes all adverse reactions under the dialysis vascular access thrombosis AMQ

[e] Rash/erythema adverse reaction includes PT rash, rash pruritic, rash macular, rash generalised, erythema.

Cancer patients

Adverse reactions were determined based on pooled data from eight randomised, double-blind, placebo-controlled studies of Aranesp with a total of 4,630 patients (Aranesp 2,888, placebo 1,742). Patients with solid tumours (e.g., lung, breast, colon, ovarian cancers) and lymphoid malignancies (e.g., lymphoma, multiple myeloma) were enrolled in the clinical studies.

Incidence of adverse reactions from controlled clinical studies and post-marketing experience are:

MedDRA system organ class	**Subject incidence**	**Adverse reaction**
Immune system disorders	Very common	Hypersensitivity[a]
Nervous system disorders	Uncommon[1]	Convulsions
Cardiac disorders	Common	Hypertension
Vascular disorders	Common	Thromboembolic events[b], including pulmonary embolism
Skin and subcutaneous tissue disorders	Common	Rash/erythema[c]
	Not known[2]	SJS/TEN, erythema multiforme, blistering, skin exfoliation
General disorders and administration site conditions	Common	Oedema[d]
	Common	Injection site pain[e]
	Uncommon[1]	Injection site bruising Injection site haemorrhage

[1] ADRs identified in the post marketing environment. Per the Guideline on Summary of Product Characteristics (Revision 2, September 2009), frequency of ADRs identified in the post marketing setting was determined using the "Rule of three".
[2] Frequency cannot be estimated from the available data.
Source: includes 8 randomised, double-blind, placebo-controlled studies (980291-schedule 1 and 2, 980297, 990114, 20000161, 20010145, 20030232, and 20070782)
[a] Hypersensitivity events includes all events under the hypersensitivity SMQ.
[b] Thromboembolic events adverse reactions includes PT embolism, thrombosis, deep vein thrombosis, jugular vein thrombosis, venous thrombosis, arterial thrombosis, pelvic venous thrombosis, peripheral embolism, pulmonary embolism, as well as thrombosis in device from SOC product issues.
[c] Rash adverse reactions includes PT rash, rash pruritic, rash generalised, rash papular, erythema, exfoliative rash, rash maculo-papular, rash vesicular as well as rash pustular from SOC Infections and Infestations.
[d] Oedema: includes PT Oedema Peripheral, Oedema, Generalised Oedema, Oedema due to Cardiac Disease, Face oedema
[e] Injection site pain adverse reaction includes PT injection site pain, administration site pain, catheter site pain, infusion site pain and vessel puncture site pain.

Description of selected adverse reactions

Chronic renal failure patients

Stroke was reported as common in CRF patients in TREAT (see section 5.1).

In isolated cases, neutralising anti-erythropoietin antibody mediated pure red cell aplasia (PRCA) associated with Aranesp therapy have been reported predominantly in patients with CRF treated subcutaneously. In case PRCA is diagnosed, therapy with Aranesp must be discontinued and patients should not be switched to another recombinant erythropoietic protein (see section 4.4).

The frequency of all hypersensitivity reactions was estimated from clinical trial data as very common in CRF patients. Hypersensitivity reactions were also very common in the placebo groups. There have been reports, from post-marketing experience, of serious hypersensitivity reactions including anaphylactic reaction, angioedema, allergic bronchospasm, skin rash and urticaria associated with darbepoetin alfa.

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 (see section 4.4).

Convulsions have been reported in patients receiving darbepoetin alfa (see section 4.4). The frequency is estimated from clinical trial data as uncommon in CRF patients.

In CRF patients on haemodialysis, events of vascular access thrombosis (such as vascular access complication, arteriovenous fistula thrombosis, graft thrombosis, shunt thrombosis, arteriovenous fistula site complication, etc.) have been reported in post-marketing data. The frequency is estimated from clinical trial data as uncommon.

Cancer patients

Hypertension has been observed in cancer patients in post-marketing experience (see section 4.4). The frequency is estimated from clinical trial data as common in cancer patients and was also common in the placebo groups.

Hypersensitivity reactions have been observed in cancer patients in post-marketing experience. The frequency of all hypersensitivity reactions was estimated from clinical trial data as very common in cancer patients. Hypersensitivity reactions were also very common in the placebo groups. There have been reports of serious hypersensitivity reactions including anaphylactic reaction, angioedema, allergic bronchospasm, skin rash and urticaria associated with darbepoetin alfa.

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 (see section 4.4).

Convulsions have been reported in patients receiving darbepoetin alfa in post-marketing experience (see section 4.4). The frequency is estimated from clinical trial data as uncommon in cancer patients. Convulsions were common in the placebo groups.

Paediatric chronic renal failure population

In all paediatric CRF studies, there were no additional adverse reactions identified for paediatric patients compared to those previously reported for adult patients (see section 5.1).

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:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

The maximum amount of Aranesp that can be safely administered in single or multiple doses has not been determined. Therapy with Aranesp can result in polycythaemia if the haemoglobin is not carefully monitored and the dose

appropriately adjusted. Cases of severe hypertension have been observed following overdose with Aranesp (see section 4.4).

In the event of polycythaemia, Aranesp should be temporarily withheld (see section 4.2). If clinically indicated, phlebotomy may be performed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-anaemic preparations, other anti-anaemic preparations, ATC Code: B03XA02.

Mechanism of action

Human erythropoietin is an endogenous glycoprotein hormone that is the primary regulator of erythropoiesis through specific interaction with the erythropoietin receptor on the erythroid progenitor cells in the bone marrow. The production of erythropoietin primarily occurs in and is regulated by the kidney in response to changes in tissue oxygenation. Production of endogenous erythropoietin is impaired in patients with chronic renal failure and the primary cause of their anaemia is due to erythropoietin deficiency. In patients with cancer receiving chemotherapy the etiology of anaemia is multifactorial. In these patients, erythropoietin deficiency and a reduced response of erythroid progenitor cells to endogenous erythropoietin both contribute significantly towards their anaemia.

Pharmacodynamic effects

Darbepoetin alfa stimulates erythropoiesis by the same mechanism as the endogenous hormone. Darbepoetin alfa has five N-linked carbohydrate chains whereas the endogenous hormone and recombinant human erythropoietins (r-HuEPO) have three. The additional sugar residues are molecularly indistinct from those on the endogenous hormone. Due to its increased carbohydrate content darbepoetin alfa has a longer terminal half-life than r-HuEPO and consequently a greater *in vivo* activity. Despite these molecular changes, darbepoetin alfa retains a very narrow specificity for the erythropoietin receptor.

Clinical efficacy and safety

Chronic renal failure patients

Patients with CRF experienced greater risks for death and serious cardiovascular events when administered ESAs to target higher versus lower haemoglobin levels (13.5 g/dL (8.4 mmol/L) versus 11.3 g/dL (7.1 mmol/L); 14 g/dL (8.7 mmol/L) versus 10 g/dL (6.2 mmol/L) in two clinical studies.

In a randomised, double-blind correction study (n = 358) comparing once every two week and once monthly dosing schedules in patients with CRF not on dialysis, darbepoetin alfa once monthly dosing was non-inferior to once every two week

dosing for correcting anaemia. The median (quartile 1, quartile 3) time to achieve haemoglobin correction (≥ 10.0 g/dL and ≥ 1.0 g/dL increase from baseline) was 5 weeks for both once every two week (3, 7 weeks) and once monthly dosing (3, 9 weeks). During the evaluation period (weeks 29-33), the mean (95% CI) weekly equivalent dose was 0.20 (0.17, 0.24) mcg/kg in the once every two week arm and 0.27 (0.23, 0.32) mcg/kg in the once monthly arm.

In a randomised, double-blind, placebo-controlled study (TREAT) of 4,038 CRF patients not on dialysis with type 2 diabetes and haemoglobin levels ≤ 11 g/dL, patients received either treatment with darbepoetin alfa to target haemoglobin levels of 13 g/dL or placebo (with darbepoetin alfa rescue at haemoglobin less than 9 g/dL). The study did not meet either primary objective of demonstrating a reduction in risk for all-cause mortality or cardiovascular morbidity (darbepoetin alfa vs placebo; HR 1.05, 95% CI (0.94, 1.17)), or all-cause mortality or end stage renal disease (ESRD) (darbepoetin alfa vs placebo; HR 1.06, 95% CI (0.95, 1.19)). Analysis of the individual components of the composite endpoints showed the following HR (95% CI): death 1.05 (0.92, 1.21), congestive heart failure (CHF) 0.89 (0.74, 1.08), myocardial infarction (MI) 0.96 (0.75, 1.23), stroke 1.92 (1.38, 2.68), hospitalisation for myocardial ischaemia 0.84 (0.55, 1.27), ESRD 1.02 (0.87, 1.18).

Pooled post-hoc analyses of clinical studies of ESAs have been performed in 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 sections 4.2 and 4.4).

Paediatric population

In a randomised clinical study 114 paediatric patients aged 2 to 18 with chronic kidney disease receiving or not receiving dialysis who were anaemic (haemoglobin < 10.0 g/dL) and not being treated with an ESA were administered darbepoetin alfa weekly (n = 58) or once every two weeks (n = 56) for the correction of anaemia. Haemoglobin concentrations were corrected to ≥ 10 g/dL in > 98% ($p < 0.001$) of paediatric patients administered darbepoetin alfa once weekly and 84% ($p = 0.293$) once every two weeks. At the time haemoglobin ≥ 10.0 g/dL was first achieved, the mean (SD) weight-adjusted dose was 0.48 (0.24) mcg/kg (range: 0.0 to 1.7 mcg/kg) weekly for the once weekly group and 0.76 (0.21) mcg/kg (range: 0.3 to 1.5 mcg/kg) biweekly for the once every two week group.

In a clinical study in 124 paediatric patients with chronic kidney disease receiving or not receiving dialysis aged 1 to 18, patients that were stable on epoetin alfa were randomised to receive either darbepoetin alfa administered once weekly (subcutaneously or intravenously) using a dose conversion ratio of 238:1 or to continue with epoetin alfa therapy at the current dose, schedule, and route of administration. The primary efficacy endpoint [change in haemoglobin between baseline and the evaluation period (week 21-28)] was comparable between the two groups. The mean haemoglobin for r-HuEPO and darbepoetin alfa at baseline was 11.1 (SD 0.7) g/dL and 11.3 (SD 0.6) g/dL, respectively. The mean haemoglobin at week 28 for r-HuEPO and darbepoetin alfa was 11.1 (SD 1.4) g/dL and 11.1 (SD 1.1) g/dL, respectively.

In an European observational registry study which enrolled 319 paediatric patients with chronic kidney disease (13 (4.1%) patients < 1 year of age, 83 (26.0%) patients 1-< 6 years of age, 90 (28.2%) patients 6-< 12 years of age, and 133 (41.7%) patients

≥ 12 years of age) receiving darbepoetin alfa, mean haemoglobin concentrations ranging between 11.3 and 11.5 g/dL and mean weight-adjusted darbepoetin alfa doses remained relatively constant (between 2.31 mcg/kg month and 2.67 mcg/kg month) over the study period for the entire study population.

In these studies, no meaningful differences were identified between the safety profile for paediatric patients and that previously reported for adult patients (see section 4.8).

Cancer patients receiving chemotherapy

EPO-ANE-3010, 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 (SOC) as compared with SOC 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 SOC arm (5.8% versus 11.4%); however, significantly more patients had thrombotic vascular events in the epoetin alfa plus SOC arm (2.8% versus 1.4%). At the final analysis, 1,653 deaths were reported. Median overall survival in the epoetin alfa plus SOC group was 17.8 months compared with 18.0 months in the SOC 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 SOC group and 7.5 months in the SOC 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 SOC group and 8.3 months in the SOC group (HR 1.033, 95% CI: 0.924, 1.156).

In a prospective, randomised double-blind, placebo-controlled study conducted in 314 lung cancer patients receiving platinum containing chemotherapy there was a significant reduction in transfusion requirements ($p < 0.001$).

Clinical studies have demonstrated that darbepoetin alfa had similar effectiveness when administered as a single injection either once every three weeks, once every two weeks, or weekly without any increase in total dose requirements.

The safety and effectiveness of once every three weeks dosing of Aranesp therapy in reducing the requirement for red blood cell transfusions in patients undergoing chemotherapy was assessed in a randomised, double-blind, multinational study. This study was conducted in 705 anaemic patients with non-myeloid malignancies receiving multi-cycle chemotherapy. Patients were randomised to receive Aranesp at 500 mcg once every three weeks or 2.25 mcg/kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 mcg in the once every three weeks group and 1.35 mcg/kg in the once weekly group) if haemoglobin increased by more than 1 g/dL in a 14-day period. In the once every three weeks group, 72% of patients required dose reductions. In the once weekly group, 75% of patients required dose reductions. This study supports 500 mcg once every three weeks being comparable to once weekly administration with

respect to the incidence of subjects receiving at least one red blood cell transfusion from week 5 to the end of treatment phase.

In a prospective, randomised double-blind, placebo-controlled study conducted in 344 anaemic patients with lymphoproliferative malignancies receiving chemotherapy there was a significant reduction in transfusion requirements and an improvement in haemoglobin response ($p < 0.001$). Improvement in fatigue, as measured by the Functional Assessment of Cancer Therapy-fatigue (FACT-fatigue) scale, was also observed.

Erythropoietin is a growth factor that primarily stimulates red blood cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells.

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

In a randomised, double-blind, placebo-controlled phase 3 study 2,549 adult patients with anaemia receiving chemotherapy for the treatment of advanced stage non-small cell lung cancer (NSCLC), were randomised 2:1 to darbepoetin alfa or placebo and treated to a maximum Hb of 12 g/dL. The results showed non-inferiority for the primary endpoint of overall survival with a median survival for darbepoetin alfa versus placebo of 9.5 and 9.3 months, respectively (stratified HR 0.92; 95% CI: 0.83–1.01). The secondary endpoint of progression free survival was 4.8 and 4.3 months, respectively (stratified HR 0.95; 95% CI: 0.87–1.04), ruling out the pre-defined 15% risk increase.

A systematic review has also been performed involving more than 9,000 cancer patients participating in 57 clinical trials. Meta-analysis of overall survival data produced a hazard ratio point estimate of 1.08 in favour of controls (95% CI: 0.99, 1.18; 42 trials and 8,167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06; 35 trials and 6,769 patients) was observed in patients treated with recombinant human erythropoietin. There is therefore consistent evidence to suggest that there may be significant harm to patients with cancer who are treated with recombinant human erythropoietin. The extent to which these outcomes might apply to the administration of recombinant human erythropoietin to patients with cancer, treated with chemotherapy to achieve haemoglobin concentrations less than 13 g/dL, is unclear because few patients with these characteristics were included in the data reviewed.

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

5.2 Pharmacokinetic properties

Due to its increased carbohydrate content the level of darbepoetin alfa in the circulation remains above the minimum stimulatory concentration for erythropoiesis for longer than the equivalent molar dose of r-HuEPO, allowing darbepoetin alfa to be administered less frequently to achieve the same biological response.

Chronic renal failure patients

The pharmacokinetics of darbepoetin alfa has been studied clinically in chronic renal failure patients following intravenous and subcutaneous administration. The terminal half-life of darbepoetin alfa is 21 hours (SD 7.5) when administered intravenously. Clearance of darbepoetin alfa is 1.9 mL/hr/kg (SD 0.56) and the volume of distribution (V_{ss}) is approximately equal to plasma volume (50 mL/kg). Bioavailability is 37% with subcutaneous administration. Following monthly administration of darbepoetin alfa, at subcutaneous doses ranging from 0.6 to 2.1 mcg/kg, the terminal half-life was 73 hours (SD 24). The longer terminal half-life of darbepoetin alfa administered subcutaneously compared to intravenously is due to subcutaneous absorption kinetics. In clinical studies, minimal accumulation was observed with either route of administration. In preclinical studies it has been shown that renal clearance is minimal (up to 2% of total clearance), and does not affect the serum half-life.

Data from 809 patients receiving Aranesp in European clinical studies were analysed to assess the dose required to maintain haemoglobin; no difference was observed between the average weekly dose administered via the intravenous or subcutaneous routes of injection.

The pharmacokinetics of darbepoetin alfa in paediatric patients (2 to 16 years) with CRF who were either receiving or not receiving dialysis was assessed for sampling periods up to 2 weeks (336 hours) after one or two subcutaneous or intravenous doses. Where the same sampling duration was used, observed pharmacokinetic data and population pharmacokinetic modelling demonstrated that the pharmacokinetics of darbepoetin alfa was similar for paediatric and adult patients with CRF.

In a phase 1 pharmacokinetic study, following intravenous administration, an approximate 25% difference between paediatric and adult patients in the area under the curve from time 0 to infinity (AUC[0-∞]) was observed; however,

this difference was less than the 2-fold range in AUC(0-∞) observed for the paediatric patients. AUC(0-∞) was similar between adult and paediatric patients with CRF following subcutaneous administration. Half-life was also similar between adult and paediatric patients with CRF following both intravenous and subcutaneous administration.

Cancer patients receiving chemotherapy

Following subcutaneous administration of 2.25 mcg/kg to adult cancer patients a mean peak concentration of 10.6 ng/mL (SD 5.9) of darbepoetin alfa was reached at a mean time of 91 hours (SD 19.7). These parameters were consistent with dose linear pharmacokinetics over a wide dose range (0.5 to 8 mcg/kg weekly and 3 to 9 mcg/kg every two weeks). Pharmacokinetic parameters did not change on multiple dosing over 12 weeks (dosing every week or every two weeks). There was an expected moderate (< 2 fold) increase in serum concentration as steady state was approached, but no unexpected accumulation upon repeated administration. A pharmacokinetic study in patients with chemotherapy-induced anaemia treated with 6.75 mcg/kg darbepoetin alfa administered SC every 3 weeks in combination with chemotherapy was conducted which allowed for full characterisation of the terminal half-life. In this study, mean (SD) terminal half-life was 74 (SD 27) hours.

5.3 Preclinical safety data

In all studies in rats and dogs darbepoetin alfa produced marked increases in haemoglobin, haematocrits, red blood cell counts and reticulocytes, which correspond to the expected pharmacological effects. Adverse events at very high doses were all considered to be related to an exaggerated pharmacological effect (decreased tissue perfusion due to increased blood viscosity). These included myelofibrosis and splenic hypertrophy as well as broadening of the ECG-QRS complex in dogs but no dysrhythmia and no effect on the QT interval were observed.

Darbepoetin alfa did not reveal any genotoxic potential nor did it have any effect on the proliferation of non-haematological cells *in vitro* or *in vivo*. In the chronic toxicity studies no tumourigenic or unexpected mitogenic responses were observed in any tissue type. The carcinogenic potential of darbepoetin alfa has not been evaluated in long-term animal studies.

In studies performed in rats and rabbits no clinically relevant evidence of harmful effects with respect to pregnancy, embryonal/ foetal development, parturition or postnatal development was observed. Placental transfer was minimal. No alteration of fertility was detected.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate monobasic
Sodium phosphate dibasic
Sodium chloride
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of incompatibility studies, this medicinal product must not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Keep the container in the outer carton in order to protect from light.

For the purpose of ambulatory use, Aranesp may be removed from storage once for a maximum single period of seven days at room temperature (up to 25ºC). Once removed from the refrigerator and has reached room temperature (up to 25ºC) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Aranesp 10 micrograms solution for injection in pre-filled syringe
0.4 mL solution for injection (25 mcg/mL darbepoetin alfa) in a type 1 glass pre-filled syringe with stainless steel 27 gauge needle. Pack size of 1 or 4 pre-filled syringes.
Aranesp 20 micrograms solution for injection in pre-filled syringe
0.5 mL solution for injection (40 mcg/mL darbepoetin alfa) in a type 1 glass pre-filled syringe with stainless steel 27 gauge needle. Pack size of 1 or 4 pre-filled syringes.
Aranesp 30 micrograms solution for injection in pre-filled syringe
0.3 mL solution for injection (100 mcg/mL darbepoetin alfa) in a type 1 glass pre-filled syringe with stainless steel 27 gauge needle. Pack size of 1 or 4 pre-filled syringes.

Aranesp 40 micrograms solution for injection in pre-filled syringe
0.4 mL solution for injection (100 mcg/mL darbepoetin alfa) in a type 1 glass pre-filled syringe with stainless steel 27 gauge needle. Pack size of 1 or 4 pre-filled syringes.
Aranesp 50 micrograms solution for injection in pre-filled syringe
0.5 mL solution for injection (100 mcg/mL darbepoetin alfa) in a type 1 glass pre-filled syringe with stainless steel 27 gauge needle. Pack size of 1 or 4 pre-filled syringes.
Aranesp 60 micrograms solution for injection in pre-filled syringe
0.3 mL solution for injection (200 mcg/mL darbepoetin alfa) in a type 1 glass pre-filled syringe with stainless steel 27 gauge needle. Pack size of 1 or 4 pre-filled syringes.
Aranesp 80 micrograms solution for injection in pre-filled syringe
0.4 mL solution for injection (200 mcg/mL darbepoetin alfa) in a type 1 glass pre-filled syringe with stainless steel 27 gauge needle. Pack size of 1 or 4 pre-filled syringes.
Aranesp 100 micrograms solution for injection in pre-filled syringe
0.5 mL solution for injection (200 mcg/mL darbepoetin alfa) in a type 1 glass pre-filled syringe with stainless steel 27 gauge needle. Pack size of 1 or 4 pre-filled syringes.
Aranesp 130 micrograms solution for injection in pre-filled syringe
0.65 mL solution for injection (200 mcg/mL darbepoetin alfa) in a type 1 glass pre-filled syringe with stainless steel 27 gauge needle. Pack size of 1 or 4 pre-filled syringes.
Aranesp 150 micrograms solution for injection in pre-filled syringe
0.3 mL solution for injection (500 mcg/mL darbepoetin alfa) in a type 1 glass pre-filled syringe with stainless steel 27 gauge needle. Pack size of 1 or 4 pre-filled syringes.
Aranesp 300 micrograms solution for injection in pre-filled syringe
0.6 mL solution for injection (500 mcg/mL darbepoetin alfa) in a type 1 glass pre-filled syringe with stainless steel 27 gauge needle. Pack size of 1 or 4 pre-filled syringes.
Aranesp 500 micrograms solution for injection in pre-filled syringe
1 mL solution for injection (500 mcg/mL darbepoetin alfa) in a type 1 glass pre-filled syringe with stainless steel 27 gauge needle. Pack size of 1 or 4 pre-filled syringes.

The syringes may be presented in either blistered (1- and 4-pack), with or without an automatic needle guard or non-blistered packaging (1-pack only).

The needle cap of the pre-filled syringe contains dry natural rubber (a derivative of latex). See section 4.4.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The carton contains a package leaflet with the full instructions for use and handling.

Aranesp is a sterile but unpreserved product. Do not administer more than one dose. Any medicinal product remaining should be disposed of.

Before administration the Aranesp solution should be inspected for visible particles. Only solutions which are colourless, clear or slightly opalescent, should be injected. Do not shake. Allow the container to reach room temperature before injecting.

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

7 MARKETING AUTHORISATION HOLDER

Amgen Limited
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Milton Road
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CB4 0WA
Cambridge
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

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