For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

Cresp®

Darbepoetin alfa (r-DNA origin)

Solution for Injection in Vials and Pre-filled Syringes

Composition

Active ingredient: darbepoetin alfa (r-DNA origin)

A single-dose vial of Cresp® comes in a vial that contains either 25, 40, 60, 100, 150, 200, 300 or 500 micrograms (mcg) of the active substance darbepoetin alfa.

A single-dose pre-filled syringe of Cresp® comes in a pre-filled syringe that contains either 25, 40, 60, 100, 150, 200, 300 or 500 micrograms (mcg) of the active substance darbepoetin alfa.

Excipients: Sodium phosphate monobasic monohydrate, Sodium phosphate dibasic anhydrous, Sodium chloride, Polysorbate 80, and Water for injection. The preparation is a clear, colorless liquid, supplied in sterile preservative-free, non- pyrogenic single dose vials and pre-filled syringes.

Properties and effects

Cresp® is an erythropoiesis stimulating protein closely related to erythropoietin that is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology. Cresp® is a 165-amino acid protein that differs from recombinant human erythropoietin in containing 5 N-linked oligosaccharide chains, whereas recombinant human erythropoietin contains 3.[1] The 2 additional N-glycosylation sites result from amino acid substitutions in the erythropoietin peptide backbone. The additional carbohydrate chains increase the approximate molecular weight of the glycoprotein from 30,000 to 37,000 daltons. Cresp® is formulated as a sterile, colorless, preservative-free protein solution for subcutaneous (SC) administration.

Mechanism of Action

Darbepoetin alfa stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. A primary growth factor for erythroid development, erythropoietin is produced in the kidney and released into the bloodstream in response to hypoxia. In responding to hypoxia, erythropoietin interacts with progenitor stem cells to increase red blood cell (RBC) production. Production of endogenous erythropoietin is impaired in patients with chronic renal failure (CRF), and erythropoietin deficiency is the primary cause of their anemia. Increased hemoglobin levels are not generally observed until 2 to 6 weeks after initiating treatment with darbepoetin alfa. In patients with cancer receiving concomitant chemotherapy, the etiology of anemia is multifactorial.

Pharmacokinetics

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 subcutaneous administration. Following monthly administration of darbepoetin alfa, at subcutaneous doses ranging from 0.6 to 2.1 µg/kg, the terminal half-life was 73 hours (SD 24) with a bioavailability of 37%. 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 darbepoetin alfa in European clinical studies were analysed to assess the dose required to maintain haemoglobin. Assessment of the pharmacokinetics of darbepoetin alfa in paediatric patients (3 to 16 years) with CRF who were either receiving or not receiving dialysis determined pharmacokinetic profiles for sampling periods up to 1 week (168 hours) after a single subcutaneous dose. Compared with pharmacokinetic data from adults with CRF where the same sampling duration was used, the comparison showed that the pharmacokinetics of darbepoetin alfa were similar for paediatric and adult patients with CRF. Following subcutaneous administration, the area under the curve from time 0 to infinity (AUC[0-∞]) and the half life were similar between adult and paediatric patients with CRF.

Cancer patients receiving chemotherapy

Following subcutaneous administration of 2.25 µg/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 µg/kg weekly and 3 to 9 µg/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 µg/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.

Indications and usage

- ❖ Treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adults and paediatric patients, including patients on dialysis and patients not on dialysis.
- ❖ Treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

Posology & Method of administration

Darbepoetin alfa treatment should be initiated by physicians experienced in the above mentioned indications. Darbepoetin alfa is supplied in a vial and ready for use in a pre-filled syringe. The instructions for use, handling and disposal are given in section below "Special precautions for disposal".

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. Darbepoetin alfa should be administered subcutaneously in order to increase haemoglobin to not greater than 12 g/dl (7.5 mmol/l). Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10 g/dl (6.2 mmol/l) to 12 g/dl (7.5 mmol/l). A sustained haemoglobin level of greater than 12 g/dl (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 darbepoetin alfa is divided into two stages – correction and maintenance phase. Guidance is given separately for adult and paediatric patients. Treatment of paediatric patients younger than 1 year of age has not been studied.

Adult patients with chronic renal failure

Correction Phase

The initial dose by subcutaneous administration is 0.45 µg/kg body weight, as a single injection once weekly. Alternatively, in patients not on dialysis, an initial dose of 0.75 µg/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%. 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 the maintenance phase, darbepoetin alfa 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 darbepoetin alfa should initially receive a dose equivalent to twice the previous once weekly dose. In patients not on dialysis, once the target haemoglobin has been achieved with once every two week dosing, darbepoetin alfa may 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. Patients should be monitored closely to ensure that the lowest approved dose of darbepoetin alfa is used to provide adequate control of the symptoms of anaemia. 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. 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 darbepoetin alfa. The initial weekly dose of darbepoetin alfa (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 200. The initial every other week dose of darbepoetin alfa (µg/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 darbepoetin alfa for r-HuEPO the haemoglobin should be monitored every one or two weeks and the same route of administration should be used.

Paediatric patients with chronic renal failure

Correction Phase

For patients ≥ 11 years of age, the initial dose by subcutaneous administration is 0.45 µg/kg body weight, as a single injection once weekly. Alternatively, in patients not on dialysis, an initial dose of 0.75 µg/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. No guidance regarding the correction of haemoglobin is available for paediatric patients 1 to 10 years of age.

Maintenance Phase

For paediatric patients ≥ 11 years of age, in the maintenance phase, darbepoetin alfa 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 darbepoetin alfa should initially receive a dose equivalent to twice the previous once weekly dose. In patients not on dialysis, once the target haemoglobin has been achieved with once every two week dosing, darbepoetin alfa may be administered subcutaneously once monthly using an initial dose equal to twice the previous once every two week dose. For pediatric patients 1-18 years of age, clinical data in paediatric patients has demonstrated that patients receiving r-HuEPO two or

three times weekly may be converted to once weekly darbepoetin alfa, and those receiving r-HuEPO once weekly may be converted to once every other week darbepoetin alfa. The initial weekly pediatric dose of darbepoetin alfa (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. The initial every other week dose of Darbepoetin alfa (µg/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 darbepoetin alfa 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 should be monitored closely to ensure that the lowest approved dose of darbepoetin alfa is used to provide adequate control of the symptoms of anaemia. 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.

Treatment of symptomatic chemotherapy induced anaemia in cancer patients

Darbepoetin alfa 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 µg (6.75µg/kg) given once every three weeks, or once weekly dosing can be given at 2.25 µg/kg body weight. If the clinical response of the patient (fatigue, haemoglobin response) is inadequate after nine weeks, further therapy may not be effective. Darbepoetin alfa 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 darbepoetin alfa is used to maintain haemoglobin at a level that controls the symptoms of anaemia. Appropriate dose titration between 500 µg, 300 µg, and 150 µg 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 darbepoetin alfa 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%.

Contraindications

- ❖ Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.
- ❖ Poorly controlled hypertension.

Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of darbepoetin alfa 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 darbepoetin alfa (see section "Posology and method of administration"). 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 darbepoetin alfa should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents (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. Pure red cell aplasia caused by neutralising anti-erythropoietin antibodies has been reported in association with ESAs, including darbepoetin alfa. 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 darbepoetin alfa (see section "undesirable effects"). A paradoxical decrease in haemoglobin and development of severe anaemia associated with low reticulocyte counts should prompt to discontinue treatment with epoetin and perform antierythropoietin 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 darbepoetin alfa, therefore no data is 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, darbepoetin alfa should be used with caution in patients with liver disease. Darbepoetin alfa should also be used with caution in those patients with sickle cell anaemia or epilepsy. Misuse of darbepoetin alfa 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 cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions. In patients with chronic renal failure, maintenance haemoglobin concentration should not exceed the upper limit of the target haemoglobin concentration recommended in section "Posology and method of administration". In clinical studies, an increased risk of death, serious cardiovascular events, and vascular access thrombosis was observed when erythropoiesis-stimulating agents (ESAs) were administered to target a haemoglobin of greater than 12 g/dl (7.5 mmol/l). Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when haemoglobin concentration is increased beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion. Darbepoetin alfa should be used with caution in patients with epilepsy. Convulsions have been reported in patients receiving darbepoetin alfa.

Chronic renal failure patients

Supplementary iron therapy is recommended for all patients with serum ferritin values below 100 µg/l or whose transferrin saturation is below 20%. In patients with chronic renal failure and clinical evidence of ischaemic heart disease or congestive heart failure, the target haemoglobin should be determined individually. In these patients an upper limit of 12 g/dl (7.5 mmol/l) should be aimed for, unless severe symptoms (e.g. angina) dictate otherwise. Serum potassium levels should be monitored regularly during darbepoetin alfa therapy. Potassium elevation has been reported in a few patients receiving darbepoetin alfa, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing darbepoetin alfa 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 darbepoetin alfa and other erythropoiesis-stimulating agents (ESAs) have shown:

- ❖ shortened time to tumour progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a haemoglobin of greater than 14 g/dl (8.7 mmol/l), 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.

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 . 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 “Posology and method of administration” 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.

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 drugs that are highly bound to red blood cells e.g. cyclosporin, tacrolimus. If darbepoetin alfa is given concomitantly with any of these drugs, blood levels of these drugs should be monitored and the dosage adjusted as the haemoglobin rises.

Pregnancy and lactation

For darbepoetin alfa no clinical data on exposed pregnancies are available. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women. As there is no clinical experience with lactating women darbepoetin alfa should not be administered to women who are breast-feeding. When darbepoetin alfa therapy is absolutely indicated women must stop breastfeeding.

Effects on ability to drive and use machines

There have been no observed effects with darbepoetin alfa on the ability to drive and use machines.

Undesirable effects

General

There have been repo rts of serious allergic reactions including anaphylactic reaction, angioedema, allergic bronchospasm dyspnoea, skin rash and urticaria associated with darbepoetin alfa.

Clinical Trial Experience

Chronic renal failure patients Data presented from controlled studies included 1357 patients, 766 who received darbepoetin alfa and 591 patients who received r-HuEPO. In the darbepoetin alfa group, 83% were receiving dialysis and 17% were not receiving dialysis. Injection site pain was reported as attributable to treatment in studies when darbepoetin alfa was administered via subcutaneous injection. This was seen more frequently than with r-HuEPO. The injection site discomfort was generally mild and transient in nature and occurred predominantly after the first injection.

Incidence of undesirable effects considered related to treatment with darbepoetin alfa from controlled clinical studies are:

MedDRA system organ class	Subject Incidence	Adverse Drug Reaction
Cardiac Disorders	Very Common (≥ 1/10)	Hypertension
Skin and Subcutaneous Tissue Disorders	Common (≥ 1/100 to < 1/10)	Rash/Erythema
Vascular disorders	Uncommon (≥ 1/1,000 to < 1/100)	Thromboembolic Events
General Disorders and Administration Site Conditions	Common (≥ 1/100 to < 1/10)	Injection site pain

Cancer patients

Adverse reactions were determined based on pooled data from seven randomised, double-blind, placebo-controlled studies of darbepoetin alfa with a total of 2112 patients (darbepoetin alfa 1200, placebo 912).

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 undesirable effects considered related to treatment with darbepoetin alfa from controlled clinical studies are:

MedDRA system organ class	Subject Incidence	Adverse Drug Reaction
Skin and Subcutaneous Tissue Disorders	Common (≥ 1/100 to < 1/10)	Rash/Erythema
Vascular disorders	Common (≥ 1/100 to < 1/10)	Thromboembolic events, including pulmonary embolism
General Disorders and Administration Site Conditions	Very Common (≥ 1/10)	Oedema
	Common (≥ 1/100 to < 1/10)	Injection site pain

Post-marketing experience

The following adverse reactions have been identified during postmarketing use of darbepoetin alfa:

- Pure Red Cell Aplasia. In isolated cases, neutralising anti-erythropoietin antibody mediated pure red cell aplasia (PRCA) associated with darbepoetin alfa therapies have been reported predominantly in patients with CRF treated subcutaneously. In case PRCA is diagnosed, therapy with darbepoetin alfa must be discontinued and patients should not be switched to another recombinant erythropoietic protein (see section "special warnings").
- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.
- Convulsions.

Overdose

The therapeutic margin of darbepoetin alfa is very wide. Even at very high serum levels, no symptoms of overdose have been observed. In the event of polycythaemia, darbepoetin alfa should be temporarily withheld (see section "Posology and method of administration"). If clinically indicated, phlebotomy may be performed.

Incompatibilities

In the absence of incompatibility studies, darbepoetin alfa should not be mixed or administered as an infusion with other medicinal products.

Shelf life

24 months.

Special precautions for storage

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

Nature and contents of container

Darbepoetin alfa Injection Vials

The package of Dr. Reddy's darbepoetin alfa Injection contains six vials with any one of following strengths:

01.	Cresp® 25 Each 1 mL Single-dose vial contains: Darbepoetin alfa (r-DNA Origin) 25 mcg
02.	Cresp® 40 Each 1 mL Single-dose vial contains: Darbepoetin alfa (r-DNA Origin) 40 mcg
03.	Cresp® 60 Each 1 mL Single-dose vial contains: Darbepoetin alfa (r-DNA Origin) 60 mcg
04.	Cresp® 100 Each 1 mL Single-dose vial contains: Darbepoetin alfa (r-DNA Origin) 100 mcg
05.	Cresp® 150 Each 0.75 mL Single-dose vial contains: Darbepoetin alfa (r-DNA Origin) 150 mcg
06.	Cresp® 200 Each 1 mL Single-dose vial contains: Darbepoetin alfa (r-DNA Origin) 200 mcg
07.	Cresp® 300 Each 1 mL Single-dose vial contains: Darbepoetin alfa (r-DNA Origin) 300 mcg
08.	Cresp® 500 Each 1 mL Single-dose vial contains: Darbepoetin alfa (r-DNA Origin) 500 mcg

One labeled vial is Packed in an inner Carton along with one leaflet. Six such inner cartons are packed in one outer carton. The vials are USP type1 glass and stoppered with 13 mm coated chloro butyl stoppers, which are sealed with lacquered aluminium flip-off seal.

Darbepoetin alfa Injection Prefilled syringes

The package of darbepoetin alfa injection contains six prefilled syringes with the strengths of one of the following:

01.	Cresp® 25 Each 0.42 ml Single-dose Prefilled Syringe contains: Darbepoetin alfa (r-DNA Origin) 25 mcg
02.	Cresp® 40 Each 0.4 ml Single-dose Prefilled Syringe contains: Darbepoetin alfa (r-DNA Origin) 40 mcg
03.	Cresp® 60 Each 0.3 ml Single-dose Prefilled Syringe contains: Darbepoetin alfa (r-DNA Origin) 60 mcg
04.	Cresp® 100 Each 0.5 mL Single-dose Prefilled Syringe contains: Darbepoetin alfa (r-DNA Origin) 100 mcg
05.	Cresp® 150 Each 0.3 ml Single-dose Prefilled Syringe contains: Darbepoetin alfa (r-DNA Origin) 150 mcg
06.	Cresp® 200 Each 0.4 ml Single-dose Prefilled Syringe contains: Darbepoetin alfa (r-DNA Origin) 200 mcg
07.	Cresp® 300 Each 0.6 mL Single-dose Prefilled Syringe contains: Darbepoetin alfa (r-DNA Origin) 300 mcg
08.	Cresp® 500 Each 1.0 mL Single-dose Prefilled Syringe contains: Darbepoetin alfa (r-DNA Origin) 500 mcg

The pre-printed darbepoetin alfa PFS label with batch details is affixed on the 1 ml syringe barrel and the approved labeled PFS is fixed with the plunger rod. Then the plunger rod fixed PFS is inserted into the Preventis and then kept inside the Ecobliss card. One such qualified pre-filled syringe in Ecobliss card along with one PIL is placed into one inner carton. Six such inner cartons are packed in one outer carton.

Each pre-filled syringe is equipped with a needle shield that covers the needle. The syringe is equipped with self locking preventis for prevention of needle pricks. The syringes are made from USP type 1 glass with stainless steel hypodermic needles. The needle shield of the pre-filled syringe contains elastomeric closure conforming to the requirements of EP. Not all packs may be marketed.

Special precautions for disposal

Darbepoetin alfa is a sterile but unpreserved product. Do not administer more than one dose per syringe or vial. Any medicinal product remaining in the pre-filled syringe or vial should be disposed off. Before administration the darbepoetin alfa solution should be inspected for visible particles. Only solutions which are colourless, clear or slightly opalescent should be injected. Do not shake. Allow the prefilled syringe/vial to reach room temperature before injecting. Rotate the injection sites and inject slowly to avoid discomfort at the site of injection. Any unused product or waste material should be disposed of in accordance with local

requirements.

PATIENT INFORMATION

Please read this leaflet carefully before you start using this medicine.

Keep this leaflet. You may need to read it again. If you have any further questions, please ask your doctor. This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet

1. WHAT CRESP® IS AND WHAT IS IT USED FOR?

Your doctor has given you Cresp®(darbepoetin alfa), an anti anaemic, to treat your anaemia. Anaemia is when your blood does not contain enough red blood cells and the symptoms may be fatigue, weakness and shortness of breath.

Cresp® works in exactly the same way as the natural hormone erythropoietin. Erythropoietin is produced in your kidneys and encourages your bone marrow to produce more red blood cells. The active substance in Cresp® is darbepoetin alfa which is produced by recombinant DNA-technology in Chinese Hamster Ovary Cells.

If you have chronic renal failure

Cresp® is used to treat symptomatic anaemia that is associated with chronic renal failure (kidney failure) in adults and children. In kidney failure, the kidney does not produce enough of the natural hormone erythropoietin which can often cause anaemia.

Because it will take your body some time to make more red blood cells, it will be about four weeks before you notice any effect. Your normal dialysis routine will not affect the ability of Cresp® to treat your anaemia.

If you are receiving chemotherapy

Cresp® is used to treat symptomatic anaemia in adult cancer patients with non-bone marrow cancers (non-myeloid malignancies) who are receiving chemotherapy.

One of the main side effects of chemotherapy is that it stops the bone marrow producing enough blood cells. At first, only white blood cells seem to be affected. This is because the red blood cells have a much longer life span in the circulating blood. Towards the end of your chemotherapy course, particularly if you have had a lot of chemotherapy, your red blood cell count may fall making you anaemic.

2. BEFORE YOU USE CRESP®

DO NOT use Cresp®:

- if you have been diagnosed with high blood pressure which is not being controlled with other medicines prescribed by your doctor; or
- if you are allergic to Cresp® (darbepoetin alfa), r-HuEPO or to any of the other ingredients in Cresp®.

Take special care with Cresp®

Please tell your doctor if you are suffering or have suffered from:

- high blood pressure which is being controlled with medicines prescribed by your doctor;
- sickle cell anaemia;
- epileptic fits (seizures);
- convulsions (fits or seizures);
- liver disease;
- significant lack Of response to drugs used to treat anaemia; or
- an allergy to latex (the needle cover on the pre-filled syringe contains a derivative of latex).

Special warnings

- If you have symptoms which include unusual tiredness and a lack of energy this could mean you have pure red cell aplasia (PRCA), which has been reported in patients. PRCA means that the body has stopped or reduced the production of red blood cells which causes severe anaemia. If you experience these symptoms you should contact your doctor who will determine the best course of action to treat your anaemia.
- Your doctor should try to keep your haemoglobin between 10 and 12 g/dl.
- If you have chronic renal failure there is an increased risk of serious problems with your heart or blood vessels (cardiovascular events) if your haemoglobin is kept too high.
- If you are a cancer patient you should be aware that Cresp® may act as a cancer growth factor. Please discuss this with your doctor.
- Misuse by healthy people can cause life-threatening problems with the heart or blood vessels.

Using other medicines

Cyclosporin and tacrolimus may be affected by the number of red cells in your blood. It is important to tell your doctor if you are taking either of these drugs. Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Using Cresp® with food and drink

Food and drink do not affect Cresp®.

Pregnancy and breast-feeding

Cresp® has not been tested in pregnant women. It is important to tell your doctor if you:

- are pregnant;
- think you may be pregnant; or

❖ plan to get pregnant.
It is not known whether darbepoetin alfa is excreted in human milk. You must stop breast-feeding if you use Cresp®.

Driving and using machines
Cresp® should not affect your ability to drive or use machinery.

3. HOW TO USE CRESP®
Following blood tests, your doctor has decided you need Cresp® as your haemoglobin level is 10 g/dl or less. Your doctor will tell you how much and how often you must take Cresp® in order to maintain a haemoglobin level between 10 and 12 g/dl. This may vary depending on whether you are an adult or a child.

Injecting Cresp® yourself
Your doctor may decide that it is best for you or a carer to inject Cresp®. Your doctor will show you how to inject yourself with the pre-filled syringe. Do not try to inject yourself if you have not been trained.

If you have chronic renal failure
Cresp® is given as a single injection, either once a week, once every two weeks, or once every month under your skin (subcutaneous) In order to correct your anaemia, your initial dose of Cresp® per kilogram of your body weight will be either:
❖ 0.75 micrograms once every two weeks, or
❖ 0.45 micrograms once weekly
Your doctor will take regular blood samples to measure how your anaemia is responding and may adjust your dose once every four weeks as necessary. Once your anaemia is corrected, your doctor will continue to regularly check your blood and your dose may be adjusted further in order to maintain long-term control of your anaemia. Your doctor will inform you if your dose changes. Your blood pressure will also be checked regularly, particularly at the beginning of your treatment. In some cases, your doctor may recommend that you take iron supplements. If your doctor has decided to change your treatment from r-HuEPO (erythropoietin produced by gene technology) to Cresp®, they will choose whether you should receive your Cresp® injection once weekly or once every two weeks. The route of injection may or may not be the same as with r-HuEPO but your doctor will tell you how much you should take, and when, and may adjust your dose if necessary.

If you are receiving chemotherapy
Cresp® is given as a single injection, either once a week or once every three weeks, under your skin. In order to correct your anaemia, your initial dose will be:
❖ 500 micrograms once every three weeks (6.75 micrograms of Cresp® per kilogram of your body weight), or
❖ 2.25 micrograms (once weekly) of Cresp® per kilogram of your body weight.
Your doctor will take regular blood samples to measure how your anaemia is responding and may adjust your dose as necessary. Your treatment will continue until approximately four weeks after the end of your chemotherapy. Your doctor will tell you exactly when to stop taking Cresp®. In some cases, your doctor may recommend that you take iron supplements.

If you use more Cresp® than you should
You should have no serious problems if you take more Cresp® than you need. However, you should contact your doctor if this does happen. If you feel unwell in any way you should contact your doctor immediately.

If you forget to inject Cresp®
If you have forgotten a dose of Cresp®, you should contact your doctor to discuss when you should inject the next dose.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Cresp® may cause side effects, although not everybody gets them. The following side effects have been experienced by some patients taking Cresp®: Very Common (seen in more than 10 in 100 people)
❖ High blood pressure (hypertension)
❖ Fluid retention (oedema)

Common (seen in more than 1 in 100 people)
❖ Blood clots (thrombosis)
❖ Pain around the area injected v High blood pressure (hypertension)
❖ Headaches
❖ Joint pain (arthralgia)
❖ Fluid retension

Rare (seen in more than 1 in 10,000 people)
❖ Serious allergic reactions
❖ Shortness of breath (dyspnoea)
❖ Skin rash
❖ Hives (urticaria)

Very rare (seen in less than 1 in 10,000 people)
❖ Pure red cell aplasia (PRCA) – (anaemia, unusual tiredness, lack of energy)
❖ Convulsions (fits and seizures)
If you have any of these symptoms or you notice any side effects that are not mentioned in this leaflet, please tell your doctor.

5. HOW TO STORE CRESP®
Keep out of the reach and sight of children. Keep in the original package in order to protect from light. Store in a refrigerator (2°C – 8°C). Do not freeze. Do not use Cresp® if you think it has been frozen. Do not use Cresp® after the expiry date which is stated on the carton and on the pre-filled syringe or vial label after expiry date. The expiry date refers to the last day of that month.

6. FURTHER INFORMATION
What Cresp® contains
Cresp® comes in a pre-filled syringe or vial that contains either 25, 40, 60, 100, 150, 200, 300 or 500 micrograms of the active substance darbepoetin alfa. Cresp® also contains Sodium phosphate monobasic monohydrate, Sodium phosphate dibasic anhydrous, Sodium chloride, Polysorbate 80, and Water for injection.

What Cresp® looks like and contents of the pack

Cresp® is a clear, colourless liquid. If it is cloudy or there are particles in it, you must not use it. A single vial is packed in one inner carton. Six such inner cartons are packed in one outer carton. A single prefilled syringe is packed in one inner carton. Six such inner cartons are packed in one outer carton. Manufacturer:

Dr.Reddy's Laboratories Limited.,
Biotechnology Division,
Survey No.47, Bachupally Village, Qutubullapur Mandal, Ranga Reddy District, Andhra Pradesh - 500090, India. Telephone No.: +91 40 2304 2004 Fax No. : +91 40 2304 1418

7. INSTRUCTIONS FOR INJECTING WITH THE CRESP® PRE-FILLED SYRINGE

This section contains information on how to give yourself an injection of Cresp®. It is important that you do not try to give yourself the injection unless you have received training from your doctor. If you have questions about how to inject, please ask your doctor for assistance.

How do you or the person injecting you, use the Cresp® pre-filled syringe?

Your doctor has prescribed a Cresp® pre-filled syringe for injection into the tissue just under the skin. Your doctor will tell you how much Cresp® you need and how frequently it should be injected.

Equipment:

To give yourself an injection you will need:

- ❖ a new Cresp® pre-filled syringe; and
- ❖ alcohol wipes or similar.

What should I do before I give myself a subcutaneous injection of Cresp®?

1. Remove the pre-filled syringe from the refrigerator. Leave the pre-filled syringe at room temperature for approximately 30 minutes. This will make the injection more comfortable. Do not warm Cresp® in any other way (for example, do not warm it in a microwave or in hot water). Additionally, do not leave the syringe exposed to direct sunlight. 2. Do not shake the pre-filled syringe. 3. **Do not** remove the cover from the syringe until you are ready to inject. 4. Check that it is the correct dose that your doctor has prescribed. 5. Check the expiry date on the pre-filled syringe label (Expiry date). Do not use it if the date has passed the last day of the month shown. 6. Check the appearance of Cresp®. It must be a clear, colourless liquid. If it is cloudy or there are particles in it, you must not use it. **7. Wash your hands thoroughly.** 8. Find a comfortable, well-lit, clean surface and put all the equipment you need within reach.

How do I prepare my Cresp® injection?

Before you inject Cresp® you must do the following:

1. To avoid bending the needle,

gently pull the cover from the needle without twisting

as shown in pictures 1 and 2.

2. Do not touch the needle or push the plunger.

3. You may notice a small air bubble in the pre-filled syringe.

You do not have to remove the air bubble before injecting.

Injecting the solution with the air bubble is harmless.

4. You can now use the pre-filled syringe.

Where should I give my injection?

The best places to inject yourself are the top of your thighs and the abdomen. If someone else is injecting for you, they can also use the back of your arms. You may change the injection site if you notice the area is red or sore.

How do I give my injection?

1. Disinfect your skin by using an alcohol wipe and pinch (without squeezing)

the skin between your thumb and forefinger. 2 Put the needle fully into the

skin as shown by your nurse or doctor. 3. Pull slightly on the plunger to

check that a blood vessel has not been punctured. If you see blood in the syringe,

pull the needle out and re-insert it in another place. 4. Push the plunger with a slow

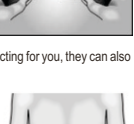
constant pressure, always keeping your skin pinched, until the syringe is empty.

5. Remove the needle and let go of your skin. 6. If you notice a spot of blood you

may gently dab it away with a cotton ball or tissue. Do not rub the injection site. If needed,

you may cover the injection site with a plaster. 7. Only use each syringe for one injection.

Do not use any Cresp® that is left in the syringe.



Remember: If you have any problems, please do not be afraid to ask your doctor for help and advice.

References 1. Egrie JC and Browne JK. Development and characterization of novel erythropoiesis stimulating protein (NESP). Brit J Cancer. 2001;84(Suppl 1):3-10.

For further information write to:
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