ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nespo 10 micrograms solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 10 micrograms of darbepoetin alfa in 0.4 ml (25 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo is supplied ready for use in a pre-filled syringe. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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

Adverse reactions were determined based on pooled data from seven randomised, double-blind, placebo-controlled studies of Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients. 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a syringe has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled syringe(s) of a 10 µg Nespo solution for injection in 0.4 ml (25 µg/ml).

The syringes may be presented in either blistered (1- & 4-pack) or non-blistered packaging (1-pack only).

The syringes are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

Nespo is a sterile but unpreserved product. Do not administer more than one dose per syringe. Any medicinal product remaining in the pre-filled syringe should be disposed of.

Before administration the Nespo solution should be inspected for visible particles. Only solutions which are colourless, clear or slightly opalescent, should be injected. Do not shake. Allow the pre-filled syringe 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.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/001 1 Pack Blister
EU/1/01/184/002 4 Pack Blister
EU/1/01/184/033 1 Pack Unblistered

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 15 micrograms solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 15 micrograms of darbepoetin alfa in 0.375 ml (40 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo is supplied ready for use in a pre-filled syringe. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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

Adverse reactions were determined based on pooled data from seven randomised, double-blind, placebo-controlled studies of Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients. 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a syringe has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled syringe(s) of a 15 µg Nespo solution for injection in 0.375 ml (40 µg/ml).

The syringes may be presented in either blistered (1- & 4-pack) or non-blistered packaging (1-pack only).

The syringes are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

Nespo is a sterile but unpreserved product. Do not administer more than one dose per syringe. Any medicinal product remaining in the pre-filled syringe should be disposed of.

Before administration the Nespo solution should be inspected for visible particles. Only solutions which are colourless, clear or slightly opalescent, should be injected. Do not shake. Allow the pre-filled syringe 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.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/003 1 Pack Blister
EU/1/01/184/004 4 Pack Blister
EU/1/01/184/034 1 Pack Unblistered

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 20 micrograms solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 20 micrograms of darbepoetin alfa in 0.5 ml (40 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo is supplied ready for use in a pre-filled syringe. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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

Adverse reactions were determined based on pooled data from seven randomised, double-blind, placebo-controlled studies of Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients. 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a syringe has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled syringe(s) of a 20 µg Nespo solution for injection in 0.5 ml (40 µg/ml).

The syringes may be presented in either blistered (1- & 4-pack) or non-blistered packaging (1-pack only).

The syringes are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

Nespo is a sterile but unpreserved product. Do not administer more than one dose per syringe. Any medicinal product remaining in the pre-filled syringe should be disposed of.

Before administration the Nespo solution should be inspected for visible particles. Only solutions which are colourless, clear or slightly opalescent, should be injected. Do not shake. Allow the pre-filled syringe 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.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/005 1 Pack Blister
EU/1/01/184/006 4 Pack Blister
EU/1/01/184/035 1 Pack Unblistered

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 30 micrograms solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 30 micrograms of darbepoetin alfa in 0.3 ml (100 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo is supplied ready for use in a pre-filled syringe. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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

Adverse reactions were determined based on pooled data from seven randomised, double-blind, placebo-controlled studies of Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients. 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a syringe has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled syringe(s) of a 30 µg Nespo solution for injection in 0.3 ml (100 µg/ml).

The syringes may be presented in either blistered (1- & 4-pack) or non-blistered packaging (1-pack only).

The syringes are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

Nespo is a sterile but unpreserved product. Do not administer more than one dose per syringe. Any medicinal product remaining in the pre-filled syringe should be disposed of.

Before administration the Nespo solution should be inspected for visible particles. Only solutions which are colourless, clear or slightly opalescent, should be injected. Do not shake. Allow the pre-filled syringe 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.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/007 1 Pack Blister
EU/1/01/184/008 4 Pack Blister
EU/1/01/184/036 1 Pack Unblistered

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 40 micrograms solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 40 micrograms of darbepoetin alfa in 0.4 ml (100 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo is supplied ready for use in a pre-filled syringe. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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

Adverse reactions were determined based on pooled data from seven randomised, double-blind, placebo-controlled studies of Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients. 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a syringe has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled syringe(s) of a 40 µg Nespo solution for injection in 0.4 ml (100 µg/ml).

The syringes may be presented in either blistered (1- & 4-pack) or non-blistered packaging (1-pack only).

The syringes are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

Nespo is a sterile but unpreserved product. Do not administer more than one dose per syringe. Any medicinal product remaining in the pre-filled syringe should be disposed of.

Before administration the Nespo solution should be inspected for visible particles. Only solutions which are colourless, clear or slightly opalescent, should be injected. Do not shake. Allow the pre-filled syringe 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.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/009 1 Pack Blister
EU/1/01/184/010 4 Pack Blister
EU/1/01/184/037 1 Pack Unblistered

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 50 micrograms solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 50 micrograms of darbepoetin alfa in 0.5 ml (100 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo is supplied ready for use in a pre-filled syringe. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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

Adverse reactions were determined based on pooled data from seven randomised, double-blind, placebo-controlled studies of Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients. 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a syringe has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled syringe(s) of a 50 µg Nespo solution for injection in 0.5 ml (100 µg/ml).

The syringes may be presented in either blistered (1- & 4-pack) or non-blistered packaging (1-pack only).

The syringes are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

Nespo is a sterile but unpreserved product. Do not administer more than one dose per syringe. Any medicinal product remaining in the pre-filled syringe should be disposed of.

Before administration the Nespo solution should be inspected for visible particles. Only solutions which are colourless, clear or slightly opalescent, should be injected. Do not shake. Allow the pre-filled syringe 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.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/011 1 Pack Blister
EU/1/01/184/012 4 Pack Blister
EU/1/01/184/038 1 Pack Unblistered

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 60 micrograms solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 60 micrograms of darbepoetin alfa in 0.3 ml (200 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo is supplied ready for use in a pre-filled syringe. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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

Adverse reactions were determined based on pooled data from seven randomised, double-blind, placebo-controlled studies of Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients. 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a syringe has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled syringe(s) of a 60 µg Nespo solution for injection in 0.3 ml (200 µg/ml).

The syringes may be presented in either blistered (1- & 4-pack) or non-blistered packaging (1-pack only).

The syringes are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

Nespo is a sterile but unpreserved product. Do not administer more than one dose per syringe. Any medicinal product remaining in the pre-filled syringe should be disposed of.

Before administration the Nespo solution should be inspected for visible particles. Only solutions which are colourless, clear or slightly opalescent, should be injected. Do not shake. Allow the pre-filled syringe 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.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/013 1 Pack Blister
EU/1/01/184/- 014 4 Pack Blister
EU/1/01/184/039 1 Pack Unblistered

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 80 micrograms solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 80 micrograms of darbepoetin alfa in 0.4 ml (200 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo is supplied ready for use in a pre-filled syringe. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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

Adverse reactions were determined based on pooled data from seven randomised, double-blind, placebo-controlled studies of Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients. 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a syringe has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled syringe(s) of a 80 µg Nespo solution for injection in 0.4 ml (200 µg/ml).

The syringes may be presented in either blistered (1- & 4-pack) or non-blistered packaging (1-pack only).

The syringes are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

Nespo is a sterile but unpreserved product. Do not administer more than one dose per syringe. Any medicinal product remaining in the pre-filled syringe should be disposed of.

Before administration the Nespo solution should be inspected for visible particles. Only solutions which are colourless, clear or slightly opalescent, should be injected. Do not shake. Allow the pre-filled syringe 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.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/015 1 Pack Blister
EU/1/01/184/016 4 Pack Blister
EU/1/01/184/040 1 Pack Unblistered

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 100 micrograms solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 100 micrograms of darbepoetin alfa in 0.5 ml (200 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo is supplied ready for use in a pre-filled syringe. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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

Adverse reactions were determined based on pooled data from seven randomised, double-blind, placebo-controlled studies of Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients. 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a syringe has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled syringe(s) of a 100 µg Nespo solution for injection in 0.5 ml (200 µg/ml).

The syringes may be presented in either blistered (1- & 4-pack) or non-blistered packaging (1-pack only).

The syringes are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

Nespo is a sterile but unpreserved product. Do not administer more than one dose per syringe. Any medicinal product remaining in the pre-filled syringe should be disposed of.

Before administration the Nespo solution should be inspected for visible particles. Only solutions which are colourless, clear or slightly opalescent, should be injected. Do not shake. Allow the pre-filled syringe 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.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/015 1 Pack Blister
EU/1/01/184/016 4 Pack Blister
EU/1/01/184/040 1 Pack Unblistered

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 130 micrograms solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 130 micrograms of darbepoetin alfa in 0.65 ml (200 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo is supplied ready for use in a pre-filled syringe. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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

Adverse reactions were determined based on pooled data from seven randomised, double-blind, placebo-controlled studies of Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients. 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a syringe has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled syringe(s) of a 130 µg Nespo solution for injection in 0.65 ml (200 µg/ml).

The syringes may be presented in either blistered (1- & 4-pack) or non-blistered packaging (1-pack only).

The syringes are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

Nespo is a sterile but unpreserved product. Do not administer more than one dose per syringe. Any medicinal product remaining in the pre-filled syringe should be disposed of.

Before administration the Nespo solution should be inspected for visible particles. Only solutions which are colourless, clear or slightly opalescent, should be injected. Do not shake. Allow the pre-filled syringe 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.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/069 1 Pack Blister
EU/1/01/184/070 4 Pack Blister
EU/1/01/184/071 1 Pack Unblistered

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 150 micrograms solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 150 micrograms of darbepoetin alfa in 0.3 ml (500 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo is supplied ready for use in a pre-filled syringe. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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

Adverse reactions were determined based on pooled data from seven randomised, double-blind, placebo-controlled studies of Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients. 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a syringe has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled syringe(s) of a 150 µg Nespo solution for injection in 0.3 ml (500 µg/ml).

The syringes may be presented in either blistered (1- & 4-pack) or non-blistered packaging (1-pack only).

The syringes are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

Nespo is a sterile but unpreserved product. Do not administer more than one dose per syringe. Any medicinal product remaining in the pre-filled syringe should be disposed of.

Before administration the Nespo solution should be inspected for visible particles. Only solutions which are colourless, clear or slightly opalescent, should be injected. Do not shake. Allow the pre-filled syringe 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.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/019 1 Pack Blister
EU/1/01/184/020 4 Pack Blister
EU/1/01/184/042 1 Pack Unblistered

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 300 micrograms solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 300 micrograms of darbepoetin alfa in 0.6 ml (500 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo is supplied ready for use in a pre-filled syringe. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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

Adverse reactions were determined based on pooled data from seven randomised, double-blind, placebo-controlled studies of Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients. 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a syringe has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled syringe(s) of a 300 µg Nespo solution for injection in 0.6 ml (500 µg/ml).

The syringes may be presented in either blistered (1- & 4-pack) or non-blistered packaging (1-pack only).

The syringes are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

Nespo is a sterile but unpreserved product. Do not administer more than one dose per syringe. Any medicinal product remaining in the pre-filled syringe should be disposed of.

Before administration the Nespo solution should be inspected for visible particles. Only solutions which are colourless, clear or slightly opalescent, should be injected. Do not shake. Allow the pre-filled syringe 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.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/021 1 Pack Blister
EU/1/01/184/022 4 Pack Blister
EU/1/01/184/043 1 Pack Unblistered

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 500 micrograms solution for injection in a pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 500 micrograms of darbepoetin alfa in 1 ml (500 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo is supplied ready for use in a pre-filled syringe. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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

Adverse reactions were determined based on pooled data from seven randomised, double-blind, placebo-controlled studies of Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients. 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a syringe has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled syringe(s) of a 500 µg Nespo solution for injection in 1 ml (500 µg/ml).

The syringes may be presented in either blistered (1- & 4-pack) or non-blistered packaging (1-pack only).

The syringes are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

Nespo is a sterile but unpreserved product. Do not administer more than one dose per syringe. Any medicinal product remaining in the pre-filled syringe should be disposed of.

Before administration the Nespo solution should be inspected for visible particles. Only solutions which are colourless, clear or slightly opalescent, should be injected. Do not shake. Allow the pre-filled syringe 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.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/031 1 Pack Blister
EU/1/01/184/032 4 Pack Blister
EU/1/01/184/044 1 Pack Unblistered

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 15 micrograms solution for injection in a vial.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 15 micrograms of darbepoetin alfa in 1 ml (15 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in a vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo is supplied in vials. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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.

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 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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

Adverse reactions were determined based on pooled data from seven randomised, double-blind, placebo-controlled studies of Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients . 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a vial has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four clear glass vial(s) with rubber stopper(s) of 15 µg Nespo solution for injection in 1 ml (15 µg/ml).

The vials are made from type 1 glass with fluoropolymer coated rubber stoppers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Nespo is a sterile but unpreserved product. Do not administer more than one dose per vial. Any medicinal product remaining in the vial should be disposed of.

Before administration the Nespo solution should be inspected for visible particles. Only solutions which are colourless, clear or slightly opalescent, should be injected. Do not shake. Allow the 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.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/023 1 Pack
EU/1/01/184/024 4 pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 25 micrograms solution for injection in a vial.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 25 micrograms of darbepoetin alfa in 1 ml (25 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in a vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo is supplied in vials. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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.

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 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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

Adverse reactions were determined based on pooled data from seven randomised, double-blind, placebo-controlled studies of Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients . 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a vial has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four clear glass vial(s) with rubber stopper(s) of 25 µg Nespo solution for injection in 1 ml (25 µg/ml).

The vials are made from type 1 glass with fluoropolymer coated rubber stoppers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Nespo is a sterile but unpreserved product. Do not administer more than one dose per vial. Any medicinal product remaining in the vial should be disposed of.

Before administration the Nespo solution should be inspected for visible particles. Only solutions which are colourless, clear or slightly opalescent, should be injected. Do not shake. Allow the 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.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/025 1 Pack
EU/1/01/184/026 4 pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 40 micrograms solution for injection in a vial.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 40 micrograms of darbepoetin alfa in 1 ml (40 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in a vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo is supplied in vials. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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.

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 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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

Adverse reactions were determined based on pooled data from seven randomised, double-blind, placebo-controlled studies of Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients . 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a vial has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four clear glass vial(s) with rubber stopper(s) of 40 µg Nespo solution for injection in 1 ml (40 µg/ml).

The vials are made from type 1 glass with fluoropolymer coated rubber stoppers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Nespo is a sterile but unpreserved product. Do not administer more than one dose per vial. Any medicinal product remaining in the vial should be disposed of.

Before administration the Nespo solution should be inspected for visible particles. Only solutions which are colourless, clear or slightly opalescent, should be injected. Do not shake. Allow the 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.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/027 1 Pack
EU/1/01/184/028 4 pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 60 micrograms solution for injection in a vial.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 60 micrograms of darbepoetin alfa in 1 ml (60 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in a vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo is supplied in vials. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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.

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 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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

Adverse reactions were determined based on pooled data from seven randomised, double-blind, placebo-controlled studies of Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients . 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a vial has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four clear glass vial(s) with rubber stopper(s) of 60 µg Nespo solution for injection in 1 ml (60 µg/ml).

The vials are made from type 1 glass with fluoropolymer coated rubber stoppers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Nespo is a sterile but unpreserved product. Do not administer more than one dose per vial. Any medicinal product remaining in the vial should be disposed of.

Before administration the Nespo solution should be inspected for visible particles. Only solutions which are colourless, clear or slightly opalescent, should be injected. Do not shake. Allow the 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.

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/029 1 Pack
EU/1/01/184/030 4 pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 10 micrograms solution for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 10 micrograms of darbepoetin alfa in 0.4 ml (25 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in a pre-filled pen.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo (SureClick) is supplied ready for use in a pre-filled pen. The pre-filled pen is only for subcutaneous administration. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 pen 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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 Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients . 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a pre-filled pen has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled pens of a 10 µg Nespo solution for injection in 0.4 ml (25 µg/ml).

The syringes inside the pen are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled pen contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

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

The Nespo (SureClick) pre-filled pen delivers the complete dose of each presentation.

Nespo is a sterile but unpreserved product. Do not administer more than one dose per pen. Each pen may only be used once. Any medicinal product remaining in the pre-filled pen should be disposed of.

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

Rotate the injection sites to avoid discomfort at the site of injection.

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

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/045 1 pack
EU/1/01/184/057 4 pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 15 micrograms solution for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 15 micrograms of darbepoetin alfa in 0.375 ml (40 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in a pre-filled pen.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo (SureClick) is supplied ready for use in a pre-filled pen. The pre-filled pen is only for subcutaneous administration. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 pen 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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 Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients . 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a pre-filled pen has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled pens of a 15 µg Nespo solution for injection in 0.375 ml (40 µg/ml).

The syringes inside the pen are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled pen contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

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

The Nespo (SureClick) pre-filled pen delivers the complete dose of each presentation.

Nespo is a sterile but unpreserved product. Do not administer more than one dose per pen. Each pen may only be used once. Any medicinal product remaining in the pre-filled pen should be disposed of.

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

Rotate the injection sites to avoid discomfort at the site of injection.

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

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/046 1 pack
EU/1/01/184/058 4 pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 20 micrograms solution for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 20 micrograms of darbepoetin alfa in 0.5 ml (40 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in a pre-filled pen.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo (SureClick) is supplied ready for use in a pre-filled pen. The pre-filled pen is only for subcutaneous administration. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 pen 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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 Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients . 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a pre-filled pen has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled pens of a 20 µg Nespo solution for injection in 0.5 ml (40 µg/ml).

The syringes inside the pen are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled pen contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

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

The Nespo (SureClick) pre-filled pen delivers the complete dose of each presentation.

Nespo is a sterile but unpreserved product. Do not administer more than one dose per pen. Each pen may only be used once. Any medicinal product remaining in the pre-filled pen should be disposed of.

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

Rotate the injection sites to avoid discomfort at the site of injection.

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

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/047 1 pack
EU/1/01/184/059 4 pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 30 micrograms solution for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 30 micrograms of darbepoetin alfa in 0.3 ml (100 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in a pre-filled pen.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo (SureClick) is supplied ready for use in a pre-filled pen. The pre-filled pen is only for subcutaneous administration. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 pen 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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 Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients . 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a pre-filled pen has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled pens of a 30 µg Nespo solution for injection in 0.3 ml (100 µg/ml).

The syringes inside the pen are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled pen contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

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

The Nespo (SureClick) pre-filled pen delivers the complete dose of each presentation.

Nespo is a sterile but unpreserved product. Do not administer more than one dose per pen. Each pen may only be used once. Any medicinal product remaining in the pre-filled pen should be disposed of.

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

Rotate the injection sites to avoid discomfort at the site of injection.

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

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/048 1 pack
EU/1/01/184/060 4 pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 40 micrograms solution for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 40 micrograms of darbepoetin alfa in 0.4 ml (100 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in a pre-filled pen.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo (SureClick) is supplied ready for use in a pre-filled pen. The pre-filled pen is only for subcutaneous administration. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 pen 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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 Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients . 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a pre-filled pen has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled pens of a 40 µg Nespo solution for injection in 0.4 ml (100 µg/ml).

The syringes inside the pen are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled pen contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

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

The Nespo (SureClick) pre-filled pen delivers the complete dose of each presentation.

Nespo is a sterile but unpreserved product. Do not administer more than one dose per pen. Each pen may only be used once. Any medicinal product remaining in the pre-filled pen should be disposed of.

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

Rotate the injection sites to avoid discomfort at the site of injection.

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

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/049 1 pack
EU/1/01/184/061 4 pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 50 micrograms solution for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 50 micrograms of darbepoetin alfa in 0.5 ml (100 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in a pre-filled pen.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo (SureClick) is supplied ready for use in a pre-filled pen. The pre-filled pen is only for subcutaneous administration. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 pen 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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 Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients . 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a pre-filled pen has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled pens of a 50 µg Nespo solution for injection in 0.5 ml (100 µg/ml).

The syringes inside the pen are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled pen contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

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

The Nespo (SureClick) pre-filled pen delivers the complete dose of each presentation.

Nespo is a sterile but unpreserved product. Do not administer more than one dose per pen. Each pen may only be used once. Any medicinal product remaining in the pre-filled pen should be disposed of.

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

Rotate the injection sites to avoid discomfort at the site of injection.

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

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/050 1 pack
EU/1/01/184/062 4 pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 60 micrograms solution for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 60 micrograms of darbepoetin alfa in 0.3 ml (200 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in a pre-filled pen.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo (SureClick) is supplied ready for use in a pre-filled pen. The pre-filled pen is only for subcutaneous administration. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 pen 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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 Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients . 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a pre-filled pen has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled pens of a 60 µg Nespo solution for injection in 0.3 ml (200 µg/ml).

The syringes inside the pen are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled pen contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

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

The Nespo (SureClick) pre-filled pen delivers the complete dose of each presentation.

Nespo is a sterile but unpreserved product. Do not administer more than one dose per pen. Each pen may only be used once. Any medicinal product remaining in the pre-filled pen should be disposed of.

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

Rotate the injection sites to avoid discomfort at the site of injection.

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

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/051 1 pack
EU/1/01/184/063 4 pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 80 micrograms solution for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 80 micrograms of darbepoetin alfa in 0.4 ml (200 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in a pre-filled pen.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo (SureClick) is supplied ready for use in a pre-filled pen. The pre-filled pen is only for subcutaneous administration. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 pen 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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 Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients . 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a pre-filled pen has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled pens of a 80 µg Nespo solution for injection in 0.4 ml (200 µg/ml).

The syringes inside the pen are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled pen contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

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

The Nespo (SureClick) pre-filled pen delivers the complete dose of each presentation.

Nespo is a sterile but unpreserved product. Do not administer more than one dose per pen. Each pen may only be used once. Any medicinal product remaining in the pre-filled pen should be disposed of.

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

Rotate the injection sites to avoid discomfort at the site of injection.

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

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/052 1 pack
EU/1/01/184/064 4 pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 100 micrograms solution for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 100 micrograms of darbepoetin alfa in 0.5 ml (200 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in a pre-filled pen.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo (SureClick) is supplied ready for use in a pre-filled pen. The pre-filled pen is only for subcutaneous administration. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 pen 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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 Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients . 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a pre-filled pen has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled pens of a 100 µg Nespo solution for injection in 0.5 ml (200 µg/ml).

The syringes inside the pen are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled pen contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

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

The Nespo (SureClick) pre-filled pen delivers the complete dose of each presentation.

Nespo is a sterile but unpreserved product. Do not administer more than one dose per pen. Each pen may only be used once. Any medicinal product remaining in the pre-filled pen should be disposed of.

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

Rotate the injection sites to avoid discomfort at the site of injection.

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

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/053 1 pack
EU/1/01/184/065 4 pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 130 micrograms solution for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 130 micrograms of darbepoetin alfa in 0.65 ml (200 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in a pre-filled pen.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo (SureClick) is supplied ready for use in a pre-filled pen. The pre-filled pen is only for subcutaneous administration. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 pen 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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 Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients . 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a pre-filled pen has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled pens of a 130 µg Nespo solution for injection in 0.65 ml (200 µg/ml).

The syringes inside the pen are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled pen contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

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

The Nespo (SureClick) pre-filled pen delivers the complete dose of each presentation.

Nespo is a sterile but unpreserved product. Do not administer more than one dose per pen. Each pen may only be used once. Any medicinal product remaining in the pre-filled pen should be disposed of.

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

Rotate the injection sites to avoid discomfort at the site of injection.

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

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/072 1 pack
EU/1/01/184/073 4 pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 150 micrograms solution for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 150 micrograms of darbepoetin alfa in 0.3 ml (500 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in a pre-filled pen.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo (SureClick) is supplied ready for use in a pre-filled pen. The pre-filled pen is only for subcutaneous administration. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 pen 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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 Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients . 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a pre-filled pen has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled pens of a 150 µg Nespo solution for injection in 0.3 ml (500 µg/ml).

The syringes inside the pen are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled pen contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

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

The Nespo (SureClick) pre-filled pen delivers the complete dose of each presentation.

Nespo is a sterile but unpreserved product. Do not administer more than one dose per pen. Each pen may only be used once. Any medicinal product remaining in the pre-filled pen should be disposed of.

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

Rotate the injection sites to avoid discomfort at the site of injection.

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

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/054 1 pack
EU/1/01/184/066 4 pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 300 micrograms solution for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 300 micrograms of darbepoetin alfa in 0.6 ml (500 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in a pre-filled pen.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo (SureClick) is supplied ready for use in a pre-filled pen. The pre-filled pen is only for subcutaneous administration. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 pen 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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 Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients . 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a pre-filled pen has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled pens of a 300 µg Nespo solution for injection in 0.6 ml (500 µg/ml).

The syringes inside the pen are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled pen contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

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

The Nespo (SureClick) pre-filled pen delivers the complete dose of each presentation.

Nespo is a sterile but unpreserved product. Do not administer more than one dose per pen. Each pen may only be used once. Any medicinal product remaining in the pre-filled pen should be disposed of.

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

Rotate the injection sites to avoid discomfort at the site of injection.

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

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/055 1 pack
EU/1/01/184/067 4 pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Nespo 500 micrograms solution for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 500 micrograms of darbepoetin alfa in 1 ml (500 µg/ml).

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in a pre-filled pen.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

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

Nespo (SureClick) is supplied ready for use in a pre-filled pen. The pre-filled pen is only for subcutaneous administration. The instructions for use, handling and disposal are given in section 6.6.

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. Nespo 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.

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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo 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.

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 Nespo. The initial weekly dose of Nespo (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 Nespo (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 Nespo 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 or intravenous 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, Nespo 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 Nespo 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, Nespo 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 Nespo, and those receiving r-HuEPO once weekly may be converted to once every other week Nespo. The initial weekly or once every other week pediatric dose of Nespo (µg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. Because of individual variability, titration to optimal therapeutic doses is expected for individual patients. When substituting Nespo 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 Nespo 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.

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

Nespo 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 (6.75 µg/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.

Nespo 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 Nespo 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 Nespo 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%.

4.3 Contraindications

Hypersensitivity to darbepoetin alfa, r-HuEPO or any of the excipients.

Poorly controlled hypertension.

4.4 Special warnings and precautions for use

General

Blood pressure should be monitored in all patients, particularly during initiation of Nespo 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 Nespo (see section 4.2).

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 Nespo should prompt a search for causative factors. Deficiencies of iron, folic acid or vitamin B12 reduce the effectiveness of erythropoiesis stimulating agents 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 recombinant erythropoietic proteins, 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 4.8).

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

Nespo should also be used with caution in those patients with sickle cell anaemia or epilepsy.

Misuse of Nespo 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 pen 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 4.2. 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.

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

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 Nespo therapy. Potassium elevation has been reported in a few patients receiving Nespo, though causality has not been established. If an elevated or rising potassium level is observed then consideration should be given to ceasing Nespo 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 Nespo 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 (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 Nespo 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.

4.6 Pregnancy and lactation

For Nespo 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 Nespo should not be administered to women who are breast-feeding. When Nespo therapy is absolutely indicated women must stop breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

General

There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, 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 Nespo and 591 patients who received r-HuEPO. In the Nespo group, 83% were receiving dialysis and 17% were not receiving dialysis.

Injection site pain was reported as attributable to treatment in studies where Nespo 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 Nespo 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 Nespo with a total of 2112 patients (Nespo 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 Nespo 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

Postmarketing Experience

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

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

- Allergic reactions, including anaphylactic reaction, angioedema, skin rash and urticaria.

- Convulsions.

4.9 Overdose

The therapeutic margin of Nespo is very wide. Even at very high serum levels, no symptoms of overdose have been observed.

In the event of polycythaemia, Nespo 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 ATC Code: B03XA02.

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**.**

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.

Cancer patients receiving chemotherapy

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 Nespo 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 randomized to receive Nespo at 500 µg once every three weeks or 2.25 µg /kg once weekly. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 µg in the once every three weeks group and 1.35 µg /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 µg 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.

Erythropoetin 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 2833 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.

A systematic review has also been performed involving more than 9000 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 8167 patients).

An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 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.

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 µg/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 Nespo 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.

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 or intravenous 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 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 pediatricpatients . 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 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.

5.3 Preclinical safety data

In all studies in rats and dogs Nespo 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.

Nespo 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, Nespo should not be mixed or administered as an infusion with other medicinal products.

6.3 Shelf life

2 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, Nespo may be removed from storage once for a maximum single period of seven days at room temperature (up to 25°C). Once a pre-filled pen has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 7 days or disposed of.

6.5 Nature and contents of container

Package containing one or four pre-filled pens of a 500 µg Nespo solution for injection in 1 ml (500 µg/ml).

The syringes inside the pen are made from type 1 glass with stainless steel 27 gauge needles. The needle cover of the pre-filled pen contains dry natural rubber (a derivative of latex). See section 4.4.

Not all packs may be marketed.

6.6 Special precautions for disposal

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

The Nespo (SureClick) pre-filled pen delivers the complete dose of each presentation.

Nespo is a sterile but unpreserved product. Do not administer more than one dose per pen. Each pen may only be used once. Any medicinal product remaining in the pre-filled pen should be disposed of.

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

Rotate the injection sites to avoid discomfort at the site of injection.

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

7. MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/184/056 1 pack
EU/1/01/184/068 4 pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 8 June 2001
Date of last renewal: 19 May 2006

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Amgen Manufacturing Limited
PO Box 4060, Road 31 km 24.6
Juncos, PR 00777-4060
Puerto Rico

Name and address of the manufacturer responsible for batch release

Amgen Europe B.V.
Amgen European Logistics Center (ELC)
Minervum 7061
4817 ZK Breda
The Netherlands

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 3.0 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1 (20 April 2007) of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities

- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

PSURs

Paediatric specific PSUR reporting submissions to regulatory authorities will be made every 6 months for the first 2 years following approval of the expanded paediatric indicationfor NESPO in the CKD setting.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 10 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.4 ml pre-filled syringe contains 10 micrograms darbepoetin alfa (25 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe
4 single use pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/001 1 pack
EU/1/01/184/002 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
PRE-FILLED SYRINGE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nespo 10 µg injection
Darbepoetin alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dompé

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

IV/SC
0.4 ml

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
BLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 10 µg
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.4 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
UNBLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 10 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.4 ml pre-filled syringe contains 10 micrograms darbepoetin alfa (25 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/033

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
UNBLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 10 µg Injection
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.4 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 15 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.375 ml pre-filled syringe contains 15 micrograms darbepoetin alfa (40 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe
4 single use pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/003 1 pack
EU/1/01/184/004 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
PRE-FILLED SYRINGE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nespo 15 µg injection
Darbepoetin alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dompé

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

IV/SC
0.375 ml

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 15 µg
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.375

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
UNBLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 15 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.375 ml pre-filled syringe contains 15 micrograms darbepoetin alfa (40 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/034

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
UNBLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 15 µg injection
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.375 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 20 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.5 ml pre-filled syringe contains 20 micrograms darbepoetin alfa (40 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe
4 single use pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/005 1 pack
EU/1/01/184/006 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
PRE-FILLED SYRINGE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nespo 20 µg injection
Darbepoetin alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dompé

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

IV/SC
0.5 ml

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 20 µg
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
UNBLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 20 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.5 ml pre-filled syringe contains 20 micrograms darbepoetin alfa (40 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/035

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
UNBLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 20 µg injection
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 30 micrograms
solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.3 ml pre-filled syringe contains30 micrograms darbepoetin alfa (100 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe
4 single use pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/007 1 pack
EU/1/01/184/008 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
PRE-FILLED SYRINGE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nespo 30 µg injection
Darbepoetin alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dompé

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

IV/SC
0.3 ml

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 30 µg
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.3 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
UNBLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 30 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.3 ml pre-filled syringe contains 30 micrograms darbepoetin alfa (100 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/036

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS UNBLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 30 µg injection
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.3 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 40 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.4 ml pre-filled syringe contains 40 micrograms darbepoetin alfa (100 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe
4 single use pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/009 1 pack
EU/1/01/184/010 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
PRE-FILLED SYRINGE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nespo 40 µg injection
Darbepoetin alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dompé

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

IV/SC
0.4 ml

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 40 µg
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.4 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
UNBLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 40 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.4 ml pre-filled syringe contains 40 micrograms darbepoetin alfa (100 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/037

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS UNBLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 40 µg injection
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.4 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 50 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.5 ml pre-filled syringe contains 50 micrograms darbepoetin alfa (100 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe
4 single use pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/011 1 pack
EU/1/01/184/012 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
PRE-FILLED SYRINGE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nespo 50 µg injection
Darbepoetin alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dompé

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

IV/SC
0.5 ml

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 50 µg
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
UNBLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 50 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.5 ml pre-filled syringe contains 50 micrograms darbepoetin alfa (100 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/038

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS UNBLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 50 µg injection
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 60 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.3 ml pre-filled syringe contains 60 micrograms darbepoetin alfa (200 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe
4 single use pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/013 1 pack
EU/1/01/184/014 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
PRE-FILLED SYRINGE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nespo 60 µg injection
Darbepoetin alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dompé

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

IV/SC
0.3 ml

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 60 µg
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.3 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
UNBLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 60 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.3 ml pre-filled syringe contains 60 micrograms darbepoetin alfa (200 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/039

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS UNBLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 60 µg injection
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.3 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 80 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.4 ml pre-filled syringe contains 80 micrograms darbepoetin alfa (200 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe
4 single use pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/015 1 pack
EU/1/01/184/016 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
PRE-FILLED SYRINGE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nespo 80 µg injection
Darbepoetin alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dompé

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

IV/SC
0.4 ml

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 80 µg
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.4 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
UNBLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 80 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.4 ml pre-filled syringe contains 80 micrograms darbepoetin alfa (200 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/040

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS UNBLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 80 µg injection
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.4 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 100 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.5 ml pre-filled syringe contains 100 micrograms darbepoetin alfa (200 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe
4 single use pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/017 1 pack
EU/1/01/184/018 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
PRE-FILLED SYRINGE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nespo 100 µg injection
Darbepoetin alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dompé

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

IV/SC
0.5 ml

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 100 µg
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
UNBLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 100 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.5 ml pre-filled syringe contains 100 micrograms darbepoetin alfa (200 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/041

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS UNBLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 100 µg injection
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 130 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.65 ml pre-filled syringe contains 130 micrograms darbepoetin alfa (200 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe
4 single use pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/069 1 pack
EU/1/01/184/070 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
PRE-FILLED SYRINGE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nespo 130 µg injection
Darbepoetin alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dompé

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

IV/SC
0.65 ml

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 130 µg
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.65 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
UNBLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 130 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.65 ml pre-filled syringe contains 130 micrograms darbepoetin alfa (200 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/071

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS UNBLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 130 µg injection
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.65 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 150 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.3 ml pre-filled syringe contains 150 micrograms darbepoetin alfa (500 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe
4 single use pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/019 1 pack
EU/1/01/184/020 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
PRE-FILLED SYRINGE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nespo 150 µg injection
Darbepoetin alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dompé

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

IV/SC
0.3 ml

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 150 µg
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.3 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
UNBLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 150 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.3 ml pre-filled syringe contains 150 micrograms darbepoetin alfa (500 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/042

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS UNBLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 150 µg injection
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.3 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 300 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.6 ml pre-filled syringe contains 300 micrograms darbepoetin alfa (500 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe
4 single use pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/021 1 pack
EU/1/01/184/022 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
PRE-FILLED SYRINGE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nespo 300 µg injection
Darbepoetin alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dompé

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

IV/SC
0.6 ml

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 300 µg
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.6 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
UNBLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 300 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.6 ml pre-filled syringe contains 300 micrograms darbepoetin alfa (500 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/043

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS UNBLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 300 µg injection
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.6 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 500 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled syringe contains 500 micrograms darbepoetin alfa (500 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe
4 single use pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/031 1 pack
EU/1/01/184/032 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
PRE-FILLED SYRINGE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nespo 500 µg injection
Darbepoetin alfa

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dompé

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

IV/SC
1 ml

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 500 µg
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
UNBLISTERED PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 500 micrograms solution for injection in a pre-filled syringe
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled syringe contains 500 micrograms darbepoetin alfa (500 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/044

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS UNBLISTERED PRE-FILLED SYRINGE LABEL

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

Nespo 500 µg injection
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
VIAL CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 15 micrograms solution for injection in a vial
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml vial 15 micrograms darbepoetin alfa.

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use vial
4 single use vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/023 1 pack
EU/1/01/184/024 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS VIAL LABEL

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

Nespo 15 µg injection
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
VIAL CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 25 micrograms solution for injection in a vial
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml vial 25 micrograms darbepoetin alfa.

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use vial
4 single use vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/025 1 pack
EU/1/01/184/026 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS VIAL LABEL

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

Nespo 25 µg injection
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
VIAL CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 40 micrograms solution for injection in a vial
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml vial 40 micrograms darbepoetin alfa.

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use vial
4 single use vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/027 1 pack
EU/1/01/184/028 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS VIAL LABEL

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

Nespo 40 µg injection
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
VIAL CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 60 micrograms solution for injection in a vial
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml vial 60 micrograms darbepoetin alfa.

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 single use vial
4 single use vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/029 1 pack
EU/1/01/184/030 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS VIAL LABEL

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

Nespo 60 µg injection
Darbepoetin alfa
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 10 micrograms solution for injection in a pre-filled pen
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.4 ml pre-filled pen contains 10 micrograms darbepoetin alfa (25 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

SureClick x1
1 single use pre-filled pen
This box containing 1 pre-filled pen, is part of a 4-multipack
SureClick x4
4 single use pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/045 1 pack
EU/1/01/184/057 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PRE-FILLED PEN LABEL

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

Nespo 10 µg injection
Darbepoetin alfa
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.4 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 15 micrograms solution for injection in a pre-filled pen
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.375 ml pre-filled pen contains 15 micrograms darbepoetin alfa (40 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

SureClick x1
1 single use pre-filled pen
This box containing 1 pre-filled pen, is part of a 4-multipack
SureClick x4
4 single use pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/046 1 pack
EU/1/01/184/058 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PRE-FILLED PEN LABEL

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

Nespo 15 µg injection
Darbepoetin alfa
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.375 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 20 micrograms solution for injection in a pre-filled pen
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.5 ml pre-filled pen contains 20 micrograms darbepoetin alfa (40 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

SureClick x1
1 single use pre-filled pen
This box containing 1 pre-filled pen, is part of a 4-multipack
SureClick x4
4 single use pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/047 1 pack
EU/1/01/184/059 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PRE-FILLED PEN LABEL

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

Nespo 20 µg injection
Darbepoetin alfa
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 30 micrograms solution for injection in a pre-filled pen
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.3 ml pre-filled pen contains 30 micrograms darbepoetin alfa (100 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

SureClick x1
1 single use pre-filled pen
This box containing 1 pre-filled pen, is part of a 4-multipack
SureClick x4
4 single use pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/048 1 pack
EU/1/01/184/060 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PRE-FILLED PEN LABEL

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

Nespo 30 µg injection
Darbepoetin alfa
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.3 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 40 micrograms solution for injection in a pre-filled pen
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.4 ml pre-filled pen contains 40 micrograms darbepoetin alfa (100 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

SureClick x1
1 single use pre-filled pen
This box containing 1 pre-filled pen, is part of a 4-multipack
SureClick x4
4 single use pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/049 1 pack
EU/1/01/184/061 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PRE-FILLED PEN LABEL

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

Nespo 40 µg injection
Darbepoetin alfa
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.4 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 50 micrograms solution for injection in a pre-filled pen
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.5 ml pre-filled pen contains 50 micrograms darbepoetin alfa (100 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

SureClick x1
1 single use pre-filled pen
This box containing 1 pre-filled pen, is part of a 4-multipack
SureClick x4
4 single use pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/050 1 pack
EU/1/01/184/062 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PRE-FILLED PEN LABEL

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

Nespo 50 µg injection
Darbepoetin alfa
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 60 micrograms solution for injection in a pre-filled pen
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.3 ml pre-filled pen contains 60 micrograms darbepoetin alfa (200 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

SureClick x1
1 single use pre-filled pen
This box containing 1 pre-filled pen, is part of a 4-multipack
SureClick x4
4 single use pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/051 1 pack
EU/1/01/184/063 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PRE-FILLED PEN LABEL

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

Nespo 60 µg injection
Darbepoetin alfa
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.3 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 80 micrograms solution for injection in a pre-filled pen
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.4 ml pre-filled pen contains 80 micrograms darbepoetin alfa (200 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

SureClick x1
1 single use pre-filled pen
This box containing 1 pre-filled pen, is part of a 4-multipack
SureClick x4
4 single use pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/052 1 pack
EU/1/01/184/064 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PRE-FILLED PEN LABEL

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

Nespo 80 µg injection
Darbepoetin alfa
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.4 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 100 micrograms solution for injection in a pre-filled pen
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.5 ml pre-filled pen contains 100 micrograms darbepoetin alfa (200 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

SureClick x1
1 single use pre-filled pen
This box containing 1 pre-filled pen, is part of a 4-multipack
SureClick x4
4 single use pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/053 1 pack
EU/1/01/184/065 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PRE-FILLED PEN LABEL

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

Nespo 100 µg injection
Darbepoetin alfa
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 130 micrograms solution for injection in a pre-filled pen
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.65 ml pre-filled pen contains 130 micrograms darbepoetin alfa (200 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

SureClick x1
1 single use pre-filled pen
This box containing 1 pre-filled pen, is part of a 4-multipack
SureClick x4
4 single use pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/072 1 pack
EU/1/01/184/073 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PRE-FILLED PEN LABEL

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

Nespo 130 µg injection
Darbepoetin alfa
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.65 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 150 micrograms solution for injection in a pre-filled pen
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.3 ml pre-filled pen contains 150 micrograms darbepoetin alfa (500 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

SureClick x1
1 single use pre-filled pen
This box containing 1 pre-filled pen, is part of a 4-multipack
SureClick x4
4 single use pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/054 1 pack
EU/1/01/184/066 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PRE-FILLED PEN LABEL

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

Nespo 150 µg injection
Darbepoetin alfa
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.3 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 300 micrograms solution for injection in a pre-filled pen
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.6 ml pre-filled pen contains 300 micrograms darbepoetin alfa (500 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

SureClick x1
1 single use pre-filled pen
This box containing 1 pre-filled pen, is part of a 4-multipack
SureClick x4
4 single use pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/055 1 pack
EU/1/01/184/067 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PRE-FILLED PEN LABEL

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

Nespo 300 µg injection
Darbepoetin alfa
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.6 ml

6. OTHER

Dompé Biotec S.p.A.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nespo 500 micrograms solution for injection in a pre-filled pen
Darbepoetin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled pen contains 500 micrograms darbepoetin alfa (500 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

SureClick x1
1 single use pre-filled pen
This box containing 1 pre-filled pen, is part of a 4-multipack
SureClick x4
4 single use pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For subcutaneous use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/184/056 1 pack
EU/1/01/184/068 4 pack

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS PRE-FILLED PEN LABEL

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

Nespo 500 µg injection
Darbepoetin alfa
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP.:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

Dompé Biotec S.p.A.

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Nespo 10 micrograms solution for injection in a pre-filled syringe
Nespo 15 micrograms solution for injection in a pre-filled syringe
Nespo 20 micrograms solution for injection in a pre-filled syringe
Nespo 30 micrograms solution for injection in a pre-filled syringe
Nespo 40 micrograms solution for injection in a pre-filled syringe
Nespo 50 micrograms solution for injection in a pre-filled syringe
Nespo 60 micrograms solution for injection in a pre-filled syringe
Nespo 80 micrograms solution for injection in a pre-filled syringe
Nespo 100 micrograms solution for injection in a pre-filled syringe
Nespo 130 micrograms solution for injection in a pre-filled syringe
Nespo 150 micrograms solution for injection in a pre-filled syringe
Nespo 300 micrograms solution for injection in a pre-filled syringe
Nespo 500 micrograms solution for injection in a pre-filled syringe
darbepoetin alfa

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, ask your doctor, nurse or pharmacist.

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, nurse or pharmacist.

In this leaflet

1. WHAT NESPO IS AND WHAT IS IT USED FOR

Your doctor has given you Nespo (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.

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

If you have chronic renal failure

Nespo 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 Nespo to treat your anaemia.

If you are receiving chemotherapy

Nespo 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 NESPO

DO NOT use Nespo:

- 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 Nespo (darbepoetin alfa), r-HuEPO or to any of the other ingredients in Nespo.

Take special care with Nespo

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 syinge 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 Nespo may act as a blood cell growth factor and in some circumstances may have a negative impact on your cancer. Depending on your individual situation a blood transfusion may be preferable. 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 Nespo with food and drink

Food and drink do not affect Nespo.

Pregnancy and breast-feeding

Nespo 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 Nespo.

Driving and using machines

Nespo should not affect your ability to drive or use machinery.

3. HOW TO USE NESPO

Following blood tests, your doctor has decided you need Nespo as your haemoglobin level is 10 g/dl or less. Your doctor will tell you how much and how often you must take Nespoin 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 Nespo yourself

Your doctor may decide that it is best for you or a carer to inject Nespo. Your doctor, nurse or pharmacist will show you how to inject yourself with the pre-filled syringe. Do not try to inject yourself if you have not been trained. **Never inject Nespo into a vein yourself.**

If you have chronic renal failure

Nespo is given as a single injection, either once a week, once every two weeks, or once every month either under your skin (subcutaneous) or into a vein (intravenous).

In order to correct your anaemia, your initial dose of Nespo 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.

Your doctor may decide to change the way that your injection is given (either under the skin or into a vein). If this changes you will start on the same dose as you have been receiving and your doctor will take blood samples to make sure that your anaemia is still being managed correctly.

If your doctor has decided to change your treatment from r-HuEPO (erythropoietin produced by gene-technology) to Nespo, they will choose whether you should receive your Nespo injection once weekly or once every two weeks. The route of injection is 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

Nespo 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 Nespo per kilogram of your body weight), or
- 2.25 micrograms (once weekly) of Nespo 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 Nespo.

In some cases, your doctor may recommend that you take iron supplements.

If you use more Nespo than you should

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

If you forget to inject Nespo

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Nespo may cause side effects, although not everybody gets them.

The following side effects have been experienced by some patients taking Nespo:

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
- Rash and/or redness of the skin

Rare (seen in more than 1 in 10,000 people)

Serious allergic reactions which may include:
- Sudden life-threatening allergic reactions (anaphylaxis)
- Swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema)
- 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) have been reported in patients treated with Nespo.

If you have any of these symptoms or you notice any side effects that are not mentioned in this leaflet, please tell your doctor, nurse or pharmacist.

5. HOW TO STORE NESPO

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 Nespo if you think it has been frozen.

When your syringe has been removed from the refrigerator and left at room temperature for approximately 30 minutes before injection it must either be used within 7 days or disposed of.

Do not use Nespo after the expiry date which is stated on the carton and on the pre-filled pen label after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Nespo contains

Nespo comes in a pre-filled syringe that contains either 10, 15, 20, 30, 40, 50, 60, 80, 100, 130, 150, 300 or 500 micrograms of the active substance darbepoetin alfa.

Nespo also contains sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80 and water for injections.

What Nespo looks like and contents of the pack

Nespo is a clear, colourless or slightly pearly liquid. If it is cloudy or there are particles in it, you must not use it.

Nespo is available in packs of 1 or 4 pre-filled syringes (not all pack sizes may be marketed). The syringes are provided either with (1-& 4-pack) or without (1-pack) a blister-wrapping.

Marketing Authorisation Holder:
Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

Manufacturer:
Amgen Europe B.V.
Minervum 7061
NL-4817 ZK Breda
The Netherlands

Further information

If you want more information about this medicine, please contact the local representative of the company that is authorised to market Nespo.

This leaflet was last approved in .

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

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7. INSTRUCTIONS FOR INJECTING WITH THE NESPO PRE-FILLED SYRINGE

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

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

Your doctor has prescribed an Nespo pre-filled syringe for injection into the tissue just under the skin. Your doctor, nurse, or pharmacist will tell you how much Nespo you need and how frequently it should be injected.

Equipment:

To give yourself an injection you will need:

- a new Nespo pre-filled syringe; and
- alcohol wipes or similar.

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

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 Nespo 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 (EXP:). Do not use it if the date has passed the last day of the month shown.

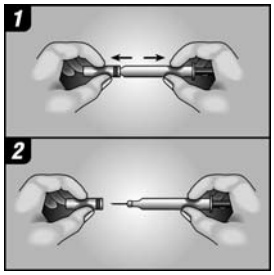
6. Check the appearance of Nespo. It must be a clear, colourless or slightly pearly liquid. If it is cloudy or there are particles in it, you must not use it.

7. **Wash your hands thoroughly**.

8. Find a comfortable, well-lit, clean surface and put all the equipment you need within reach.

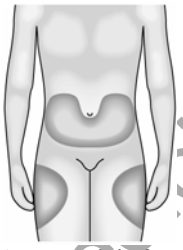
How do I prepare my Nespo injection?

Before you inject Nespo 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 arethe top of your thighs andthe 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 Nespo that is left in the syringe.

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

Disposing of used syringes

- Do not put the cover back on used needles, as you may accidentally prick yourself.
- Keep used syringes out of the reach and sight of children.
- The used pre-filled syringe should be disposed of in accordance with local requirements. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Nespo 15 micrograms solution for injection in a vial
Nespo 25 micrograms solution for injection in a vial
Nespo 40 micrograms solution for injection in a vial
Nespo 60 micrograms solution for injection in a vial
darbepoetin alfa

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, ask your doctor, nurse or pharmacist.

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, nurse or pharmacist.

In this leaflet

1. WHAT NESPO IS AND WHAT IS IT USED FOR

Your doctor has given you Nespo (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.

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

If you have chronic renal failure

Nespo 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 Nespo to treat your anaemia.

If you are receiving chemotherapy

Nespo 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 NESPO

DO NOT use Nespo:

- 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 Nespo (darbepoetin alfa), r-HuEPO or to any of the other ingredients in Nespo.

Take special care with Nespo

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

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 Nespo may act as a blood cell growth factor and in some circumstances may have a negative impact on your cancer. Depending on your individual situation a blood transfusion may be preferable. 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 Nespo with food and drink

Food and drink do not affect Nespo.

Pregnancy and breast-feeding

Nespo 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 Nespo.

Driving and using machines

Nespo should not affect your ability to drive or use machinery.

3. HOW TO USE NESPO

Following blood tests, your doctor has decided you need Nespo as your haemoglobin level is 10 g/dl or less. Your doctor will tell you how much and how often you must take Nespoin 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.

If you have chronic renal failure

Nespo is given as a single injection, either once a week, once every two weeks, or once every month either under your skin (subcutaneous) or into a vein (intravenous).

In order to correct your anaemia, your initial dose of Nespo 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.

Your doctor may decide to change the way that your injection is given (either under the skin or into a vein). If this changes you will start on the same dose as you have been receiving and your doctor will take blood samples to make sure that your anaemia is still being managed correctly.

If your doctor has decided to change your treatment from r-HuEPO (erythropoietin produced by gene-technology) to Nespo, they will choose whether you should receive your Nespo injection once weekly or once every two weeks. The route of injection is 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

Nespo 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 Nespo per kilogram of your body weight), or
- 2.25 micrograms (once weekly) of Nespo 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 Nespo.

In some cases, your doctor may recommend that you take iron supplements.

If you use more Nespo than you should

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

If you forget to inject Nespo

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Nespo may cause side effects, although not everybody gets them.

The following side effects have been experienced by some patients taking Nespo:

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
- Rash and/or redness of the skin

Rare (seen in more than 1 in 10,000 people)

Serious allergic reactions which may include:

- Sudden life-threatening allergic reactions (anaphylaxis)
- Swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema)
- 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) have been reported in patients treated with Nespo.

If you have any of these symptoms or you notice any side effects that are not mentioned in this leaflet, please tell your doctor, nurse or pharmacist.

5. HOW TO STORE NESPO

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 Nespo if you think it has been frozen.

When your vial has been removed from the refrigerator and left at room temperature for approximately 30 minutes before injection it must either be used within 7 days or disposed of.

Do not use Nespo after the expiry date which is stated on the carton and on the pre-filled pen label after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Nespo contains

Nespo comes in a vial that contains either 15, 25, 40 or 60 micrograms of the active substance darbepoetin alfa.

Nespo also contains sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80 and water for injections.

What Nespo looks like and contents of the pack

Nespo is a clear, colourless or slightly pearly liquid. If it is cloudy or there are particles in it, you must not use it.

Nespo is available in packs of 1 or 4 vials (not all pack sizes may be marketed).

Marketing Authorisation Holder:
Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

Manufacturer:
Amgen Europe B.V.
Minervum 7061

NL-4817 ZK Breda
The Netherlands

Further information

If you want more information about this medicine, please contact the local representative of the company that is authorised to market Nespo.

This leaflet was last approved in .

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

PACKAGE LEAFLET: INFORMATION FOR THE USER

Nespo 10 micrograms solution for injection in a pre-filled pen (SureClick)
Nespo 15 micrograms solution for injection in a pre-filled pen (SureClick)
Nespo 20 micrograms solution for injection in a pre-filled pen (SureClick)
Nespo 30 micrograms solution for injection in a pre-filled pen (SureClick)
Nespo 40 micrograms solution for injection in a pre-filled pen (SureClick)
Nespo 50 micrograms solution for injection in a pre-filled pen (SureClick)
Nespo 60 micrograms solution for injection in a pre-filled pen (SureClick)
Nespo 80 micrograms solution for injection in a pre-filled pen (SureClick)
Nespo 100 micrograms solution for injection in a pre-filled pen (SureClick)
Nespo 130 micrograms solution for injection in a pre-filled pen (SureClick)
Nespo 150 micrograms solution for injection in a pre-filled pen (SureClick)
Nespo 300 micrograms solution for injection in a pre-filled pen (SureClick)
Nespo 500 micrograms solution for injection in a pre-filled pen (SureClick)
darbepoetin alfa

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, ask your doctor, nurse or pharmacist.

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, nurse or pharmacist.

In this leaflet

1. WHAT NESPO IS AND WHAT IS IT USED FOR

Your doctor has given you Nespo (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.

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Nespo 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.

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If you are receiving chemotherapy

Nespo 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 NESPO

DO NOT use Nespo:

- 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 Nespo (darbepoetin alfa), r-HuEPO or to any of the other ingredients in Nespo.

Take special care with Nespo

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 pen 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 Nespo may act as a blood cell growth factor and in some circumstances may have a negative impact on your cancer. Depending on your individual situation a blood transfusion may be preferable. 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 Nespo with food and drink

Food and drink do not affect Nespo.

Pregnancy and breast-feeding

Nespo 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 Nespo.

Driving and using machines

Nespo should not affect your ability to drive or use machinery.

3. HOW TO USE THE NESPO PRE-FILLED PEN (SURECLICK)

Following blood tests, your doctor has decided you need Nespo as your haemoglobin level is 10 g/dl or less. Your injection is to be given under the skin (subcutaneous), and so you may use the Nespo pre-filled pen. Your doctor will tell you how much and how often you must take Nespoin 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 Nespo yourself

Your doctor has decided that the Nespo pre-filled pen is the best way for you, a nurse, or a carer to inject Nespo. Your doctor, nurse or pharmacist will show you how to inject yourself with the pre-filled pen. Do not try to inject yourself if you have not been trained. **Never inject Nespo into a vein yourself. The pre-filled pen is designed to inject the area under your skin only.**

For instructions on use of the pre-filled pen, please read the section at the end of this leaflet.

If you have chronic renal failure

The Nespo pre-filled pen is given as a single injection, either once a week, once every two weeks, or once every month.

In order to correct your anaemia, your initial dose of Nespo 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.

Your doctor may decide to change the way that your injection is given (either under the skin or into a vein). If this changes you will start on the same dose as you have been receiving and your doctor will take blood samples to make sure that your anaemia is still being managed correctly.

If your doctor has decided to change your treatment from r-HuEPO (erythropoietin produced by gene-technology) to Nespo, they will choose whether you should receive your Nespo injection once weekly or once every two weeks. The route of injection is 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

Nespo 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 Nespo per kilogram of your body weight, or
- 2.25 micrograms (once weekly) of Nespo 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 Nespo.

In some cases, your doctor may recommend that you take iron supplements.

If you use more Nespo than you should

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

If you forget to inject Nespo

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Nespo may cause side effects, although not everybody gets them.

The following side effects have been experienced by some patients taking Nespo:

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
- Rash and/or redness of the skin

Rare (seen in more than 1 in 10,000 people)

Serious allergic reactions which may include:

- Sudden life-threatening allergic reactions (anaphylaxis)
- Swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema)
- 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) have been reported in patients treated with Nespo.

If you have any of these symptoms or you notice any side effects that are not mentioned in this leaflet, please tell your doctor, nurse or pharmacist.

5. HOW TO STORE NESPO

Keep out of the reach and sight of children. Keep the pre-filled pen in the original package in order to protect from light.

Store in a refrigerator (2°C – 8°C). Do not freeze. Do not use Nespo if you think it has been frozen.

When your pen has been removed from the refrigerator and left at room temperature for approximately 30 minutes before injection it must either be used within 7 days or disposed of.

Do not use Nespo after the expiry date which is stated on the carton and on the pre-filled pen label after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Nespo contains

Nespo (SureClick) comes in a pre-filled pen that contains either 10, 15, 20, 30, 40, 50, 60, 80, 100, 130, 150, 300 or 500 micrograms of the active substance darbepoetin alfa.

Nespo also contains sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80 and water for injections.

What Nespo looks like and contents of the pack

Nespo is a clear, colourless or slightly pearly liquid. If it is cloudy or there are particles in it, you must not use it.

Nespo (SureClick) is available in packs containing 1 or 4 pre-filled pens (not all pack sizes may be marketed).

Marketing Authorisation Holder:
Dompé Biotec S.p.A.
Via San Martino 12
I-20122 Milan
Italy

Manufacturer:
Amgen Europe B.V.
Minervum 7061
NL-4817 ZK Breda
The Netherlands

Further information

If you want more information about this medicine, please contact the local representative of the company that is authorised to market Nespo.

This leaflet was last approved in .

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

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7. INSTRUCTIONS FOR INJECTING WITH THE NESPO PRE-FILLED PEN (SURECLICK)

This section contains information on how to properly use the Nespo pre-filled pen. It is important that you do not try to give yourself the injection unless you have received training from your doctor, nurse, or pharmacist. If you have questions about how to inject, please ask your doctor, nurse, pharmacist for assistance.

How do you, or the person injecting you, use Nespo pre-filled pen (SureClick)?

Your doctor has prescribed the Nespo pre-filled pen for injection into the tissue just under the skin. Your doctor, nurse, or pharmacist will tell you how much Nespo you need and how frequently it should be injected. Only use each pre-filled pen for one injection.

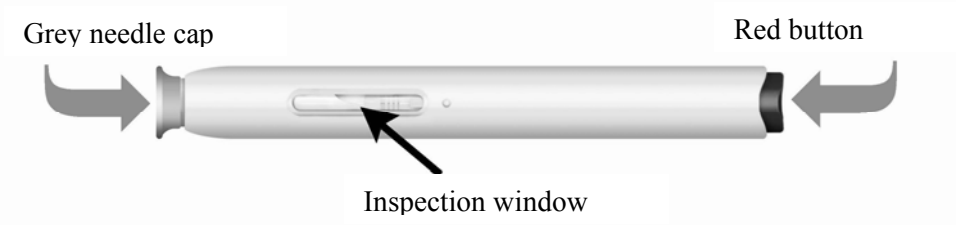
Equipment:

To give yourself an injection you will need:

- a new Nespo pre-filled pen and
- alcohol wipes or similar.

Preparing for an Nespo injection?

1. Remove the pen from the refrigerator. For a more comfortable injection, leave the pen at room temperature for approximately 30 minutes. Do not warm Nespo in any other way (for example, do not warm it in a microwave or in hot water). Additionally, do not leave the pre-filled pen exposed to direct sunlight.
2. Do not shake the pre-filled pen.
3. **Do not** remove the grey needle cap from the pre-filled pen 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 pen label (EXP:). Do not use it if the date has passed the last day of the month shown
6. Check the appearance of Nespo through the inspection window. It must be a clear, colourless or slightly pearly 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.



7a. Choosing and preparing an injection site

1. Choose an injection site

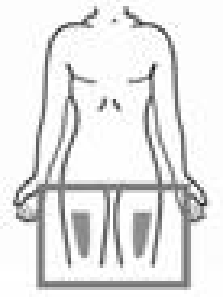
The injection site must be firm for the device to work properly.

The preferred injection site for using the Nespo pre-filled pen is the front of the thigh.

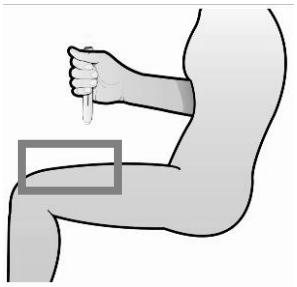
Rotate injection site:
You may rotate the site for each injection to avoid soreness at any one site.

Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks.

2a. Instructions for preferred injection site

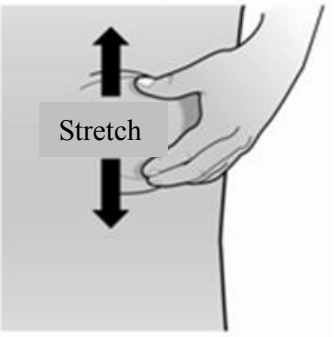


The **front of the thigh** is the preferred injection site.



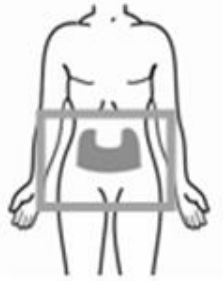
2b. Instructions for alternate injection sites

When using alternate injection sites, it is particularly important to create enough surface tension on the site to be able to successfully complete the injection.

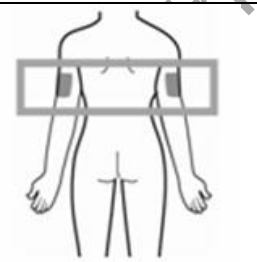


Stretch technique

Make sure that skin under and around the pre-filled pen is firm and tight to provide enough resistance to fully retract the safety guard and "unlock" the pen.



You can use the **abdomen**, except for the 2 inch/5 cm area around the belly button (navel). For the abdomen, it is recommended to lie down on your back, and stretch the skin at the injection site to create a firm and tight surface.



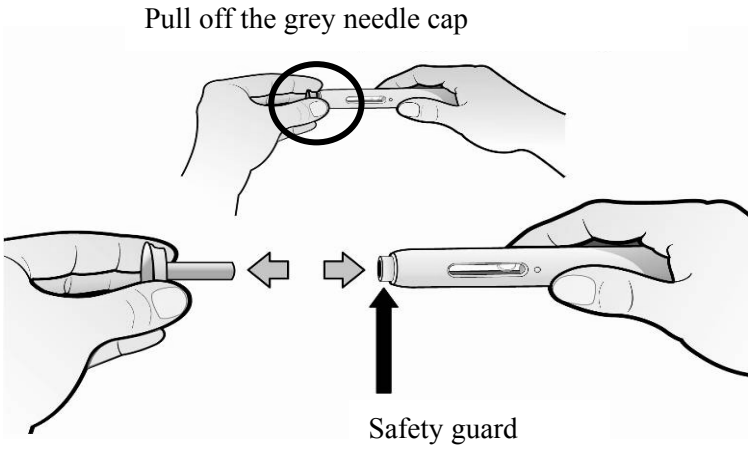
If someone else is giving you the injection, they can also use the **outer area of the upper arms**. For the upper arms, it is recommended to stretch the skin at the injection site to create a firm and tight surface.

3. Prepare the site

To prepare the area of skin where Nespo will be injected, wipe the injection site with an alcohol wipe. **Do not touch this area again before giving the injection**.

7b. Injecting Nespo using the pre-filled pen

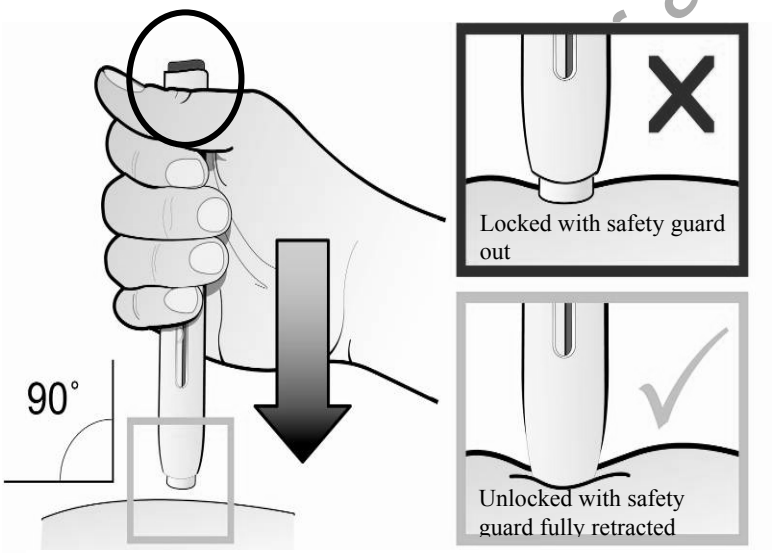
1. Pull off the grey needle cap.



∅	**Do not** twist the grey needle cap
∅	**Do not** try to put the needle cap back onto the pre-filled pen

✔	**Do** pull the grey cap straight off

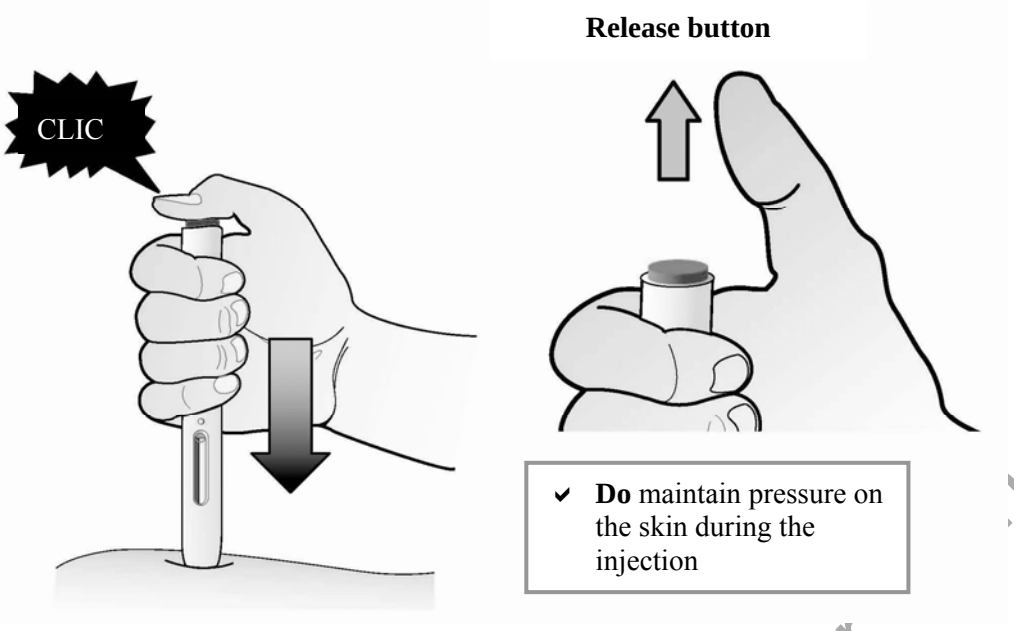
2. Do not touch the red button. Press the pre-filled pen onto the skin to unlock the safety guard.



∅	**Do not** press the red button until the safety guard is fully retracted.

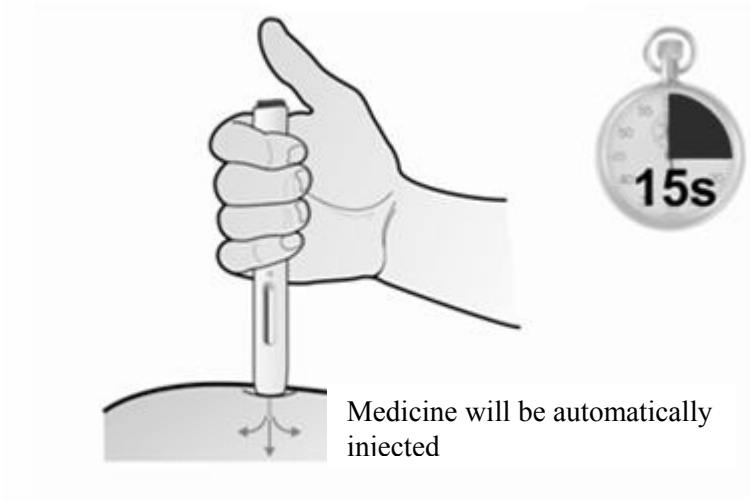
✔	**Do** keep enough downward pressure to fully retract the yellow safety guard and to keep the red button unlocked.
✔	**Do** hold the pre-filled pen at a right angle (90º) to the injection site.

3. Briefly press and release red button.



✔ **Do** maintain pressure on the skin during the injection

4. Count slowly to 15 seconds for injection to end.

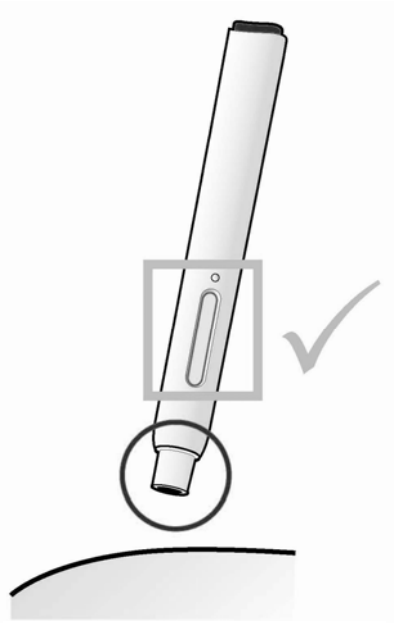


Medicine will be automatically iniected

∅ **Do not** move the pre-filled pen during the injection.

✔ **Do** wait for the injection to finish before releasing pressure.
✔ **You may hear a second click as the red button pops back up**.

5. Check window to confirm delivery of full dose



Safety guard down after use.

✔ **Do** check the inspection window to confirm it has turned yellow.

! If the inspection window is not yellow, you must contact your doctor, nurse or pharmacist.

There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site

Do not rub the injection site. If needed, you may cover the injection site with a plaster.

Remember

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

Disposing of used pre-filled pens

- The Nespo pre-filled pen should NEVER be reused.
- NEVER put the grey needle cap back into the used pre-filled pen.
- The used pre-filled pen should be disposed of in accordance with local requirements. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Optional separate additional insert:

FRONT- Nespo getting started guide:

ENGLISH	Nespo SureClick Pre-filled pen - Read package leaflet before use			
	Preferred site is front of the thigh	**Alternate sites** are the abdomen or outer area of upper arms	**Stretch the skin** on alternate injection sites Stretch Injection site must be firm and tight	Turn over for injection steps

BACK- Neso getting started guide:

ENGLISH	(1) Pull off grey needle cap ∅ Do not twist the grey needle cap	(2) Do not touch red button. Press the pen onto the skin to unlock safety guard. X Locked ✓ Unlocked	(3) Briefly press and release red button. Click Keep unlocked against skin	(4) Count slowly to 15 for injection to end.	(5) Check window ✓ Complete when yellow