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NESP® (darbepoetin alfa) Product Information

NESP® (darbepoetin alfa)

NAME OF THE DRUG

NESP® is the Kyowa Kirin Co. trademark for darbepoetin alfa (rch), a novel erythropoiesis stimulating protein produced by recombinant DNA technology.

DESCRIPTION

NESP® (darbepoetin alfa) is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. NESP® stimulates red blood cell production (erythropoiesis) by the same mechanism as recombinant human erythropoietin (r-HuEPO). NESP® is a 165-amino acid protein containing 5 N-linked oligosaccharide chains, whereas erythropoietin contains only 3. The additional carbohydrate chains increase the molecular weight of the glycoprotein to approximately 36,000 daltons.

NESP® is a sterile, clear, colourless, preservative-free aqueous solution for parenteral administration.

NESP® contains ingredients as follows:

Each injection syringe (0.5 mL) contains ingredients as follows:

Brand Name	Ingredient/content				pH value	Osmotic pressure ratio	Appearance
	Active substance		Excipient				
NESP® Injection Plastic Syringe 10 µg/ 0.5 mL	Darbepoetin alfa (Genetical recombination)	10 µg	Polysorbate 80	0.025 mg	6.0 - 6.4	About 1 (related to physiological saline)	Colourless clear solution
NESP® Injection Plastic Syringe 20 µg/ 0.5 mL		20 µg	L-methionine	0.0745 mg			
NESP® Injection Plastic Syringe 30 µg/ 0.5 mL		30 µg	Sodium dihydrogen phosphate dihydrate	1.19 mg			
NESP® Injection Plastic Syringe 40 µg/ 0.5 mL		40 µg	Sodium chloride	4.09 mg			
NESP® Injection Plastic Syringe 60 µg/ 0.5 mL		60 µg	Dibasic sodium phosphate hydrate	q.s.			
NESP® Injection Plastic Syringe 120 µg/ 0.5 mL		120 µg					
NESP® Injection Plastic Syringe 180 µg/ 0.5 mL		180 µg					

The product is available in single use pre-filled syringes.
*(*Note: Not all presentations may be available locally.)*

PHARMACOLOGY

Pharmacodynamics

Erythropoietin is a glycoprotein that is the primary regulator of erythropoiesis. The production of erythropoietin primarily occurs in the kidney and is regulated in response to changes in tissue oxygenation. Endogenous erythropoietin production is impaired in patients with chronic renal failure (CRF) and erythropoietin deficiency is the primary cause of their anaemia.

Erythropoietin acts through specific interaction with the erythropoietin receptor on erythroid progenitor cells in the bone marrow. Using a panel of human tissues neither darbepoetin alfa nor r-HuEPO (or their desialylated forms) bound to human tissues other than those expressing the erythropoietin receptor.

NESP® has been shown to stimulate erythropoiesis in anaemic CRF and cancer patients, resulting in the correction and maintenance of haemoglobin. Treatment of anaemia of CRF and cancer has been associated with a reduction in red blood cell (RBC) transfusions and improved quality of life.

In patients with cancer receiving concomitant chemotherapy, the aetiology of anaemia is multifactorial, with erythropoietin deficiency and a blunted response of erythroid progenitor cells to endogenous erythropoietin contributing significantly towards their anaemia.

Due to its increased sialic acid-containing carbohydrate content, NESP® has an approximately 3-fold longer terminal half-life than erythropoietin and consequently a greater in vivo biologic activity when administered by either the subcutaneous (SC) or intravenous (IV) route.

In cancer patients with anaemia (mean ± sd haemoglobin 9.9 ± 0.9 g/dL), a range of weekly subcutaneous doses of darbepoetin alfa from 0.5 to 8.0 µg/kg were assessed, beginning on day 1 of chemotherapy (before starting chemotherapy) and continuing for 12 weeks. Data from these studies indicate that there is a dose relationship with respect to haemoglobin response. The minimally effective starting dose with respect to reducing transfusion requirements was 1.5 µg/kg/week with a plateau observed at 4.5 µg/kg/ week.

Preclinical Experience

Darbepoetin alfa undergoes extensive metabolism, with less than 2% of intact darbepoetin alfa being excreted renally in rats, while degradation products are recovered in the urine (57% dose) and faeces (24% dose). Metabolism of darbepoetin alfa may involve desialylation by blood/tissue sialidases, with subsequent rapid removal of the desialylated form by hepatic receptors, and/or reuptake via bone marrow cells.

Pharmacokinetics

General

The concentration of darbepoetin alfa in the circulation remains above the minimum stimulatory concentration for erythropoiesis for longer than an equivalent molar dose of r-HuEPO. This allows darbepoetin alfa to be administered less frequently to achieve the same biological response. The pharmacokinetic properties of darbepoetin alfa have been studied in healthy adult subjects, in adult and paediatric CRF patients, and in adult cancer patients. In all cases darbepoetin alfa exhibits dose-linearity over the therapeutic dose range.

Subcutaneous absorption: Following SC administration in adult CRF patients, the absorption is slow and rate-limiting. The peak concentration occurs at 34 hours (range: 24 to 72 hours) post-SC administration in adult CRF patients, and bioavailability is approximately 37% (range: 30% to 50%). After SC administration of 2.25 µg/kg to adult cancer patients, darbepoetin alfa reached peak concentration at a median of 94.5 hours (range: 70.8 to 123 hours).

Distribution following intravenous administration: Distribution of darbepoetin alfa in adult CRF patients is predominantly confined to the vascular space (approximately 60 mL/kg). The distribution half-life, following IV administration, is 1.4 hours.

Elimination: In adult CRF patients, the terminal half-life of darbepoetin alfa following IV administration is approximately 21 hours (range: 12 to 40 hours). Following SC administration, the terminal half-life is 49 hours (range: 27 to 89 hours) and 39.2 hours (range: 15.5 to 54.2) in CRF and cancer patients, respectively, reflecting the long absorption half-life.

Multiple dosing: With once weekly dosing in adult CRF patients, steady-state serum concentrations are achieved within 4 weeks with < 2-fold increase in peak concentration. Accumulation was negligible following both SC and IV dosing over 1 year of treatment.

In adult cancer patients, the pharmacokinetic properties did not change with multiple dosing over 12 weeks (dosing every week or every 2 weeks). The expected moderate increases (less than 2-fold) in darbepoetin alfa serum concentrations upon multiple dosing were observed as steady state was approached. No unexpected accumulation was observed upon repeated administration of darbepoetin alfa across a wide range of doses at once weekly and once every 2 weeks dosing schedules.

Special Populations

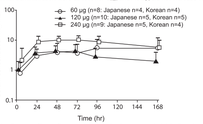
Paediatric: The pharmacokinetic parameters of darbepoetin alfa in paediatric CRF patients are similar to adult CRF patients. Following SC or IV administration in children 7 to 16 years old, the terminal half-life was 21 hours (range: 12 to 25 hours) for IV administration and 33 hours (range: 16 to 44 hours) for SC administration. The SC bioavailability was 52% (range: 32% to 70%).

Hepatic dysfunction: The efficacy and safety of darbepoetin alfa have not been established in patients with hepatic dysfunction.

Myelodysplastic Syndrome:

Single administration (Japanese and Korean patients)

Following repeated subcutaneous administration of NESP® at doses of 60-240 µg to patients with myelodysplastic syndrome for 16 weeks, the time course of serum concentrations and pharmacokinetic parameters at the initial administration were as follows. C_{max} and AUC_{0-t} did not increase in proportion to the dose.



Serum concentration-time profiles after an initial subcutaneous administration in patients with myelodysplastic syndrome (Mean ± SD)

Pharmacokinetic parameters after an initial subcutaneous administration (Mean ± SD)

Dose (µg)	Number of subjects	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-t} (ng • hr/mL)
60	8[1)]	7.044±5.149	82.84±58.18	712.7±515.9
120	10[2)]	5.061±2.271	73.36±52.87	483.8±301.2
240	9[3)]	11.730±4.116	60.84±27.42	1309.8±543.3

1) Japanese n=4, Korean n=4
2) Japanese n=5, Korean n=5
3) Japanese n=5, Korean n=4

Repeated administration (Japanese and Korean patients)

Following repeated subcutaneous administration of NESP® at doses of 60 to 240 µg to patients with myelodysplastic syndromes for 52 weeks, the serum trough concentration reached a steady state and showed no remarkable changes over the dose range tested throughout the administration period.

CLINICAL TRIAL

Clinical Experience in CRF Patients

Ten clinical studies were conducted, involving SC and IV administration of darbepoetin alfa to a total of 1578 adult CRF patients with an exposure of 942 patients years. Response to darbepoetin alfa was consistent across all studies. The time to reach the target haemoglobin is a function of the baseline haemoglobin and the rate of haemoglobin rise. The rate of increase in haemoglobin is dependent upon the dose of darbepoetin alfa administered and individual patient variation.

Maintenance in CRF Patients

Darbepoetin alfa was at least equivalent to r-HuEPO in the maintenance of a target haemoglobin (haemoglobin between 9.9-13 g/dL and between ~1.6 mL and ~1.9 mL packed cell volume) when administered either IV or SC at frequencies varying from 3 times weekly to once every 2 weeks. Ninety-seven percent of patients in the darbepoetin alfa group received their treatment at a lower frequency than they had previously received r-HuEPO, in most cases once weekly instead of 2 to 3 times weekly. The mean difference for change in haemoglobin from baseline (darbepoetin alfa minus r-HuEPO) was 0.03 g/ dL (95% confidence interval [CI]: -1.6, 2.1).

One trial evaluated 224 darbepoetin alfa-treated patients and 112 r-HuEPO-treated patients. The median darbepoetin alfa dose was 30 µg/week and the median r-HuEPO dose was 6000 U/week. The drugs were administered either IV or SC at frequencies varying from 3 times weekly to once every 2 weeks. Ninety-seven percent of patients in the darbepoetin alfa group received their treatment at a lower frequency than they had previously received r-HuEPO, in most cases once weekly instead of 2 to 3 times weekly. The mean difference for change in haemoglobin from baseline (darbepoetin alfa minus r-HuEPO) was 0.03 g/ dL (95% confidence interval [CI]: -1.6, 2.1).

In the second trial, 121 darbepoetin alfa-treated patients and 240 r-HuEPO-treated patients were evaluated. Both drugs were administered IV, darbepoetin alfa once weekly and r-HuEPO 3 times weekly. The median darbepoetin alfa dose was 38 µg/week and the median r-HuEPO dose 9900 U/week. The mean difference for change in haemoglobin from baseline (darbepoetin alfa minus r-HuEPO) was 0.16 g/dL (95% CI: -0.8, 3.3).

There were no significant differences between the drugs in the proportion of patients with unstable haemoglobin and proportion receiving blood transfusions, in either trial.

Correction of Anaemia in CRF Patients

In a trial in adult predialysis CRF patients with anaemia (haemoglobin concentration < 11 g/dL), darbepoetin alfa produced a similar response to r-HuEPO with 87% (95% CI: 80, 92) of darbepoetin alfa-treated patients (n = 129) and 86% (95% CI: 71, 95) of r-HuEPO treated patients (n = 37) achieving the haemoglobin target (> 11 g/dL and > 1 g/dL increase from baseline) after 16 weeks. The drugs were administered by the SC route. The starting dose of darbepoetin alfa was 0.45 µg/kg once weekly (approximately equivalent to 90 U/kg of r-HuEPO weekly). The starting dose of r-HuEPO was 50 U/kg twice weekly (100 U/kg total weekly dose). The doses were adjusted in ± 25% increments at 2 to 4 week intervals as required. The median time to response was 7 weeks in each group and the median doses at response were similar to the starting doses, 0.46 µg/kg/week for darbepoetin alfa and 100 U/kg/week for r-HuEPO. The median dose after 16 weeks of treatment was 0.45 µg/kg/week for darbepoetin alfa and 100 U/kg/week for r-HuEPO.

In a second trial, in adult dialysis CRF patients with anaemia (haemoglobin < 10 g/dL), r-HuEPO was started at a higher dose than darbepoetin alfa based on protein mass, 50 U/kg 3 times weekly (150 U/ kg total weekly dose) compared with 0.45 µg/kg once weekly (approximately equivalent to 90 U/kg of r-HuEPO weekly). The drugs were administered either IV or SC. A similar regime of dosage adjustments and a similar haemoglobin target were employed to the previous trial. Of patients receiving at least one dose of drug, 95% (95% CI: 77, 100) of r-HuEPO-treated patients (n = 22) and 71% (95% CI: 59, 82) of darbepoetin alfa-treated patients (n = 70) reached the haemoglobin target by 20 weeks. The median time to response was 8 weeks in the r-HuEPO group and 9 weeks in the darbepoetin alfa group and the median doses at response were 150 U/kg/week and 0.55 µg/kg/week, respectively. The median dose after 20 weeks of treatment was 0.56 µg/kg/week for darbepoetin alfa and 150 U/kg/week for r-HuEPO.

Treatment of Anaemia in Cancer Patients Receiving Chemotherapy

A randomised, double-blind, placebo-controlled, parallel-group trial was conducted in anaemic patients with lung cancer receiving multi-cycle platinum-containing chemotherapy. Randomisation was stratified by tumour type (small cell, non-small cell) and region (Australia, Canada, Central and Eastern Europe, Western Europe). The starting dose was 2.25 µg/kg/week as a single subcutaneous injection commencing on day 1 prior to administration of chemotherapy. The dose could be increased after 6 weeks up to 4.5 µg/kg/week if patients failed to achieve an increase in haemoglobin of > 1 g/L. The duration of treatment was 12 weeks.

Efficacy was determined by a reduction in the proportion of patients who were transfused over the 12-week treatment period. A significantly lower proportion of patients in the darbepoetin alfa arm, 26% (95% CI: 20, 33) required transfusion compared to 60% (95% CI: 52, 68) in the placebo arm (Kaplan-Meier estimate of proportion; p < 0.001 by Cochran-Mantel-Haenszel test) (see Table 1). There was a trend in favour of darbepoetin alfa in FACT/F, a fatigue-related quality of life score.

Table 1 Trial of darbepoetin alfa in Anaemia Associated with Chemotherapy (Modified Intention-to-Treat, Weighted by Tumour Type and Region)

Endpoint	Darbepoetin Alfa	Placebo
Number of patients Randomised Modified ITT	159 156	161 158
No. of subjects transfused over 12 weeks of treatment Kaplan-Meier (%)	53 26	89 60
Difference in proportions (%) [95% CI]	-25 [-35, -14]	

Modified ITT: ≥ 1 dose of study drug.

There were 67 patients in the darbepoetin alfa arm who had their dose increased from 2.25 to 4.5 µg/ kg/ week, at any time during the treatment period. Of the 67 patients who received a dose increase, 28% had a 2 g/dL increase in haemoglobin over baseline, generally occurring between weeks 8 to 13. Of the 89 patients who did not receive a dose increase, 69% had a 2 g/dL increase in haemoglobin over baseline, generally occurring between weeks 6 to 13.

In the same study, the effect of darbepoetin alfa on tumour progression and survival was evaluated through long-term surveillance of patients. After a median observation period of approximately 1 year, the median time to disease progression in the darbepoetin alfa group (n = 155) was 29 weeks (95% CI: 22, 33) compared with 22 weeks (95% CI: 18, 25) in the placebo group (n = 159). The median time to death in the darbepoetin alfa group was 43 weeks (95% CI: 37, not estimable) compared with 35 weeks (95% CI: 29, 48) in the placebo group.

Geriatric Use

More than 1500 darbepoetin alfa-treated patients with CRF have been studied; 28% were 65 to 74 years of age and 15% were 75 years or older. Of the 781 cancer patients in clinical studies receiving darbepoetin alfa and concomitant chemotherapy, 31% were age 65 to 74 years of age, while 12% were 75 and over. No differences in dose requirements, safety or efficacy were observed between geriatric and younger adult patients.

Multinational Clinical Study in Myelodysplastic Syndrome

NESP® was subcutaneously administered to 52 patients with myelodysplastic syndromes who were in the low or intermediate-1 risk categories under IPSS and transfusion-dependent [note 1)], with the serum erythropoietin concentration of 500 mIU (international units)/mL or lower at a dose of 60, 120, or 240µg once weekly for 48 weeks [note 2)]. The efficacy of NESP® was assessed at 16 weeks after the initiation of NESP® administration [note 3)]. In the 50 patients included in efficacy evaluation, major erythroid response [note 4)] or minor erythroid response [note 5)] was observed in 11 of 17 patients (64.7%) of the 60µg group, 8 of 18 patients (44.4%) of the 120µg group, and 10 of 15 patients (66.7%) of the 240µg group.

[note 1)] Defined as the longest transfusion-free interval of shorter than 56 days in the past 112 days (excluding transfusions performed when the haemoglobin concentration was higher than 9.0 g/dL)

[note 2)] If patients did not respond to NESP® at 16 weeks after the initiation of administration, administration of NESP® was discontinued in the 240 µg group, and the dose was increased in the other groups.

[note 3)] The target haemoglobin concentration was set at 10.0 g/dL by reference to the Guidelines for use of blood products, revised version (in Japanese) (Blood and Blood Products Division, PFSB, MHLW, 2005). To maintain the haemoglobin within the target range of 9.0 to 11.0 g/dL, administration of NESP® was suspended if the haemoglobin concentration exceeded 11.0 g/dL.

[note 4)] Defined as transfusion independence for at least 56 consecutive days during the NESP® administration period, and the mean haemoglobin concentration during the transfusion-free period of at least 1.0 g/dL higher than that at the initiation of administration.

[note 5)] Defined as 50% decrease or more in transfusion requirement in 56 consecutive days during the NESP® administration period in comparison with during the 56-day period before the initiation of administration.

Demographic and other baseline characteristics (Safety analysis set)

	Overall (N = 52)	60 µg (N = 17)	120 µg (N = 18)	240 µg (N = 17)
Gender				
Female	20 (38.5%)	6 (35.3%)	6 (33.3%)	8 (47.1%)
Male	32 (61.5%)	11 (64.7%)	12 (66.7%)	9 (52.9%)
Age (years)				
Median (min-max)	77.0 (50–89)	78.0 (50–87)	77.0 (53–89)	75.0 (50–82)
Ethnic group				
Japanese	31 (59.6 %)	10 (58.8 %)	11 (61.1 %)	10 (58.8 %)
Korean	21 (40.4 %)	7 (41.2 %)	7 (38.9 %)	7 (41.2 %)
Eastern Cooperative Oncology Group Performance Status (ECOG PS)				
0	24 (46.2 %)	8 (47.1 %)	8 (44.4 %)	8 (47.1 %)
1	27 (51.9 %)	8 (47.1 %)	10 (55.6 %)	9 (52.9 %)
2	1 (1.9 %)	1 (5.9 %)	0 (0.0 %)	0 (0.0 %)
Karyotype				
Good	43 (82.7 %)	11 (64.7 %)	16 (88.9 %)	16 (94.1 %)
Intermediate	9 (17.3 %)	6 (35.3 %)	2 (11.1 %)	1 (5.9 %)
French-American-British (FAB) classification				
RA	33 (63.5 %)	12 (70.6 %)	13 (72.2 %)	8 (47.1 %)
RARS	14 (26.9 %)	5 (29.4 %)	4 (22.2 %)	5 (29.4 %)
RAEB	5 (9.6 %)	0 (0.0 %)	1 (5.6 %)	4 (23.5 %)
2008 WHO classification				
RCUD	4 (7.7 %)	1 (5.9 %)	1 (5.6 %)	2 (11.8 %)
RARS	4 (7.7 %)	2 (11.8 %)	1 (5.6 %)	1 (5.9 %)
RCMD	31 (59.6 %)	10 (58.8 %)	13 (72.2 %)	8 (47.1 %)
RAEB-1	5 (9.6 %)	0 (0.0 %)	1 (5.6 %)	4 (23.5 %)
MDS-U	6 (11.5 %)	4 (23.5 %)	2 (11.1 %)	0 (0.0 %)
5q-syndrome	2 (3.8 %)	0 (0.0 %)	0 (0.0 %)	2 (11.8 %)
IPSS risk category				
Low	9 (17.3 %)	1 (5.9 %)	3 (16.7 %)	5 (29.4 %)
Intermediate-1	43 (82.7 %)	16 (94.1 %)	15 (83.3 %)	12 (70.6 %)
Baseline haemoglobin level (g/dL)				
Mean (SD)	7.92 (0.91)	7.69 (0.77)	8.01 (0.72)	8.04 (1.18)
Baseline Serum EPO level (mIU/mL)				
Mean (SD)	221 (134)	227 (152)	217 (116)	220 (142)
Baseline RBC transfusion (mL)				
Mean (SD)	1459 (707)	1407 (691)	1444 (825)	1527 (622)

5q-syndrome: myelodysplastic syndrome associated with isolated del(5q) chromosome abnormality
MDS-U: myelodysplastic syndrome unclassified
RA: refractory anaemia
RAEB: refractory anaemia with excess blasts
RAEB-1: refractory anaemia with excess blasts-1
RAEB-t: refractory anaemia with excess blasts in transformation
RARS: refractory anaemia with ringed sideroblasts
RCMD: refractory cytopenia with multilineage dysplasia
RCUD: refractory cytopenia with unilineage dysplasia

Proportion of patients who achieved erythroid response during the initial-dose evaluation phase* (PPS)

	Overall (N = 50)	60 µg (N = 17)	120 µg (N = 18)	240 µg (N = 15)
Major or Minor erythroid response	58.0% (29/50)	64.7% (11/17)	44.4% (8/18)	66.7% (10/15)
Major erythroid response	22.0% (11/50)	17.6% (3/17)	16.7% (3/18)	33.3% (5/15)
Minor erythroid response**	36.0% (18/50)	47.1% (8/17)	27.8% (5/18)	33.3% (5/15)

*From Week 1 to Week 16
**patients who achieved major erythroid response are excluded.

Proportion of patients who achieved erythroid response in Week 1 through Week 48 (PPS)

	Overall (N = 50)	60 µg (N = 17)	120 µg (N = 18)	240 µg (N = 15)
Major or Minor erythroid response	60.0% (30/50)	70.6% (12/17)	44.4% (8/18)	66.7% (10/15)
Major erythroid response	34.0% (17/50)	35.3% (6/17)	27.8% (5/18)	40.0% (6/15)
Minor erythroid response*	26.0% (13/50)	35.3% (6/17)	16.7% (3/18)	26.7% (4/15)

*patients achieved major erythroid response are excluded.

Proportion of patients who achieved target Hb level* during the initial-dose evaluation phase** (PPS)

Overall (N = 50)	60 µg (N = 17)	120 µg (N = 18)	240 µg (N = 15)
18.0% (9/50)	5.9% (1/17)	11.1% (2/18)	40.0% (6/15)

*10.0 g/dL
**From Week 1 to Week 16

Proportion of patients who achieved target Hb level* in Week 1 through Week 48 (PPS)

Overall (N = 50)	60 µg (N = 17)	120 µg (N = 18)	240 µg (N = 15)
28.0% (14/50)	23.5% (4/17)	16.7% (3/18)	46.7% (7/15)

*10.0 g/dL

INDICATIONS

NESP® is indicated for the treatment of anaemia associated with chronic renal failure (CRF).
NESP® is also indicated for the treatment of anaemia and reduction of transfusion requirements in patients with non-myeloid malignancies where anaemia develops as a result of concomitant administered chemotherapy.

NESP® is also indicated for anaemia with myelodysplastic syndrome. The efficacy and safety of NESP® have not been established in patients who are in the intermediate-2 or high risk categories under the International Prognostic Scoring System (IPSS). Patients indicated for NESP® should be selected based on a full knowledge of the description in the "CLINICAL TRIAL" section, including serum erythropoietin concentration in patients enrolled in clinical studies, as well as adequate understanding of the efficacy and safety of NESP® and reference to the academic guidelines and other relevant updates.

CONTRAINDICATIONS

NESP® is contraindicated in patients with:
1. Uncontrolled hypertension.
2. Known sensitivity to products derived from mammalian cells.
3. Known hypersensitivity to darbepoetin alfa or any of the excipients found in NESP®.

PRECAUTIONS

Cardiovascular and Thrombotic Events/ Increased Mortality

Cardiovascular and thrombotic events such as myocardial ischaemic and infarction, cerebrovascular haemorrhage and infarction, transient ischaemic attacks, deep venous thrombosis, arterial thrombosis, pulmonary emboli, retinal thrombosis and haemodialysis graft occlusion have been reported in patients receiving erythropoiesis stimulating agents (ESAs) such as NESP®.

ESAs have been associated with an increased risk of death and serious cardiovascular events or strokes in controlled clinical trials when administered to target a haemoglobin of greater than 12 g/ dL. There was an increased risk of serious arterial and venous thromboembolic events, including myocardial infarction, stroke, congestive heart failure, and haemodialysis graft occlusion. A rate of haemoglobin rise of greater than 1 g/dL over 2 weeks may also contribute to these risks.

To reduce cardiovascular risks, use the lowest dose of NESP® that will gradually increase the haemoglobin concentration. The haemoglobin concentration should aim not to exceed a target of 12 g/dL, the rate of haemoglobin increase should not exceed 1 g/dL in any 2-week period (see **DOSAGE AND ADMINISTRATION).**

CRF patients with relative hyporesponsiveness to ESAs may be at increased risk for mortality and cardiovascular events. These patients should be evaluated for treatable conditions (see **PRECAUTIONS: General).**

In a randomised prospective trial, 1432 anaemic chronic renal failure patients who were not undergoing dialysis were assigned to epoetin alfa treatment targeting a maintenance haemoglobin concentration of 13.5 g/dL or 11.3 g/dL. A major cardiovascular event (death, myocardial infarction, stroke, or hospitalisation for congestive heart failure) occurred among 125 (18%) of the 715 patients in the higher haemoglobin group compared to 97 (14%) among the 717 patients in the lower haemoglobin group (HR 1.3, 95% CI: 1.0, 1.7, p = 0.03).

Increased risk for serious cardiovascular events was also reported from a randomised, prospective trial of 1265 haemodialysis patients with clinically evident cardiac disease (ischaemic heart disease or congestive heart failure). In this trial, patients were assigned to epoetin alfa treatment targeted to a maintenance haemoglobin of either 14 ± 1 g/dL or 10 ± 1 g/dL. Higher mortality (35% versus 29%) was observed in the 634 patients randomised to a target haemoglobin of 14 g/dL than in the 631 patients assigned a target haemoglobin of 10 g/dL.

The reason for the increased mortality observed in this study is unknown; however, the incidence of nonfatal myocardial infarction, vascular access thrombosis, and other thrombotic events was also higher in the group randomised to a target haemoglobin of 14 g/dL.

In a randomised, double-blind, placebo-controlled study of 4,038 patients called TREAT, there was an increased risk of stroke (HR 1.92, 95% CI: 1.38, 2.68) when darbepoetin alfa was administered to anaemic patients with type 2 diabetes and CRF not on dialysis to target a haemoglobin level of 13 g/dL compared with placebo-treated patients who received darbepoetin alfa when their haemoglobin levels were less than 9 g/dL.

In a post hoc subgroup analysis of TREAT, more deaths from any cause were observed in those patients who indicated a prior history of malignancy and were treated with darbepoetin alfa to target a haemoglobin level of 13 g/dL (60 deaths out of 188 patients randomised to darbepoetin alfa vs. 37 deaths out of 160 patients randomised to placebo; HR: 1.38, 95% CI: 0.91, 2.07).

An increased incidence of thrombotic events has also been observed in patients with cancer treated with ESAs such as NESP® (see **ADVERSE REACTIONS, Adverse Events in Cancer Patients, Thrombotic Events in Cancer Patients).**

In a randomised controlled study (referred to as the 'BEST' study) with another ESA in 939 women with metastatic breast cancer receiving chemotherapy, patients received either weekly epoetin alfa or placebo for up to a year. This study was designed to show that survival was superior when an ESA was administered to prevent anaemia (maintain haemoglobin levels between 12 and 14 g/dL or haematocrit between 36% and 42%). The trial was terminated prematurely when interim results demonstrated that a higher mortality at 4 months (8.7% versus 3.4%) and a higher rate of fatal thrombotic events (1.1% versus 0.2%) in the first 4 months of the study were observed among patients treated with epoetin alfa. Based on Kaplan-Meier estimates, at the time of study termination, the 12-month survival was lower in the epoetin alfa group than in the placebo group (70% versus 76%; HR 1.37, 95% CI: 1.07, 1.75; p = 0.012).

A systematic review of 57 randomised controlled trials (including BEST and ENHANCE studies) evaluating 9353 patients with cancer compared ESAs plus RBC transfusion with RBC transfusion alone for prophylaxis or treatment of anaemia in cancer patients with or without concurrent antineoplastic therapy. An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06; 35 trials and 6769 patients) was observed in ESA-treated patients. An overall survival hazard ratio of 1.08 (95% CI: 0.99, 1.18; 42 trials and 8167 patients) was observed in ESA-treated patients.

Growth Factor Potential/ Increased Tumour Progression

NESP® is a growth factor that primarily stimulates red blood cell production. Like all growth factors, there is a theoretical concern that NESP® could act as a growth factor for any tumour type, particularly myeloid malignancies.

ESAs have been associated with shortened time to tumour progression in patients with advanced head and neck cancer receiving radiation therapy when administered to a haemoglobin between 14 to 15.5 g/ dL. NESP® should only be used to treat cancer patients with anaemia where the anaemia has arisen as a result of concomitantly administered chemotherapy.

The ENHANCE study was a randomised controlled study in 351 head and neck cancer patients where epoetin beta or placebo was administered to achieve target haemoglobins of 14 and 15 g/dL for women and men, respectively. Locoregional progression-free survival was significantly shorter in patients receiving epoetin beta, hazard ratio 1.62 (95% CI: 1.22, 2.14; p = 0.0008) with a median of 406 days epoetin beta versus 745 days placebo.

The DAHANCA 10 study, conducted in 522 patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy were randomised to darbepoetin alfa or placebo. An interim analysis in 484 patients demonstrated a 10% increase in locoregional failure rate among darbepoetin alfa-treated patients (p = 0.01). At the time of study termination, there was a trend toward worse survival in the darbepoetin alfa-treated arm (p = 0.08).

ESAs have been associated with shortened survival in patients with metastatic breast cancer receiving chemotherapy when administered to a target haemoglobin of greater than 12 g/dL.

The BEST study was previously described (see **PRECAUTIONS: Cardiovascular and Thrombotic Events/ Increased Mortality**). Mortality at 4 months (8.7% versus 3.4%) was significantly higher in the epoetin alfa arm. The most common investigator-attributed cause of death within the first 4 months was disease progression; 28 of 41 deaths in the epoetin alfa arm and 13 of 16 deaths in the placebo arm were attributed to progressive disease. Investigator assessed time to tumour progression was not different between the two groups.

Use in Cancer Patients

ESAs have been associated with an increased risk of death when administered to a haemoglobin target of 12 to 14 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. NESP® is not indicated for this population. NESP® should only be used to treat cancer patients with anaemia where the anaemia has arisen as a result of concomitantly administered chemotherapy.

In a Phase 3, double-blind, randomised (darbepoetin alfa versus placebo), 16-week study in 989 anaemic patients with active malignant disease neither receiving nor planning to receive chemotherapy or radiation therapy, there was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions. In addition, there were more deaths in the darbepoetin alfa treatment group [26% (135/515)] than the placebo group [20% (94/470)] at 16 weeks (completion of treatment phase). With a median survival follow up of 4.3 months, the absolute number of deaths was greater in the darbepoetin alfa treatment group [49% (250/515)] compared with the placebo group [46% (216/470); HR 1.29, 95% CI: 1.08, 1.55].

In a phase 3, multicentre, randomised (epoetin alfa versus placebo), double-blind study, patients with advanced non-small-cell lung cancer unsuitable for curative therapy were treated with epoetin alfa targeting haemoglobin levels between 12 and 14 g/dL. Following an interim analysis of 70 of 300 patients planned, a significant difference in median survival in favour of patients in the placebo group was demonstrated (63 versus 129 days; HR 1.84; p = 0.04).

Use in Anaemia with Myelodysplastic Syndrome

NESP® should only be administered by or under supervision of a physician with extensive expertise and experience in treating haematologic diseases and only to the patients for whom the use of NESP® is considered appropriate.

This product is intended for use in patients who have anaemia-associated problems in their daily activities. The purpose of the treatment should be to avoid blood transfusions, wean patients from transfusion-dependency, or reduce the dose of blood transfusion.

Patients should be carefully interviewed to assess the risk of reactions such as shock. Instruments and medicines for emergency treatment should be prepared beforehand in case of shock, etc. Patients should be kept calm and sufficiently monitored from the start through the end of administration. Especially, careful monitoring is required immediately after the start of administration. When treatment with NESP® is started for the first time or restarted after temporary discontinuation, it is recommended to inject intradermally a small amount of NESP® and then administer the remaining portion only after confirming that patients do not develop any abnormal reactions.

During treatment with NESP®, the haemoglobin concentration should be carefully monitored at regular intervals. Attention should be paid to prevent excessive haemoglobinosis (haemoglobin concentration >11 g/dL). (see **CLINICAL TRIAL).**

When starting NESP® or changing the dose of NESP®, measure haemoglobin concentration once a week, until haemoglobin concentration gets stable. If response of excessive haemopoiesis develops, appropriate measures such as temporary discontinuation of NESP® should be taken.

Since administration of NESP® may increase blood pressure and has been reported to cause hypertensive encephalopathy, parameters such as blood pressure, haemoglobin concentration, etc. should be closely monitored during the treatment.

Pure red cell aplasia associated with production of anti-erythropoietin antibodies may occur. Its occurrence should be suspected if anaemia is not improved or rather exacerbated during the treatment. When pure red cell aplasia is diagnosed, the treatment with NESP® should be discontinued.

Iron is an important element for exertion of the pharmacological effect of NESP®. Therefore, iron should be administered to patients with iron deficiency.

Hypertension
Patients with uncontrolled hypertension should not be treated with NESP[a]; blood pressure should be controlled adequately before initiation of therapy. Blood pressure may rise during treatment of anaemia with NESP[a]. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with darbepoetin alfa or epoetin alfa.

Special care should be taken to closely monitor and control blood pressure in patients treated with NESP[a]. During NESP[a] therapy patients should be advised of the importance of compliance with antihypertensive therapy and dietary/fluid restriction. If blood pressure is difficult to control after initiation of appropriate antihypertensive measures, the dose of NESP[a] should be reduced or temporarily withheld until haemoglobin begins to decrease (see **DOSAGE AND ADMINISTRATION**). A clinically significant change in haemoglobin may occur, but may not be observed for several weeks.

Pure Red Cell Aplasia
Pure red cell aplasia (PRCA) in association with neutralising antibodies to native erythropoietin has been observed in patients treated with ESAs, including darbepoetin alfa. This has been reported predominantly in patients with chronic renal failure receiving ESAs by subcutaneous administration. PRCA has also been reported in patients receiving ESAs for anaemia related to hepatitis C treatment (an indication for which NESP[a] is not approved).

Any patient with loss of response to NESP[a] should be investigated for the typical causes of loss of effect (see **PRECAUTIONS: General**). NESP[a] should be discontinued in any patient with evidence of PRCA and the patient evaluated for the presence of binding and neutralising antibodies to NESP[a], native erythropoietin, and any other recombinant erythropoietin administered to the patient. In patients with PRCA secondary to neutralising antibodies to any ESAs, NESP[a] should not be administered. Patients should not be switched to other ESAs as antibodies may cross-react with other erythropoietins.

Convulsions
NESP[a] should be used with caution in patients with a history of convulsions. Cases of convulsions have been very rarely reported in patients with CRF receiving darbepoetin alfa.

General
In order to ensure effective erythropoiesis, iron status should be evaluated for all patients before and during treatment, as the majority of patients will eventually require supplemental iron therapy. As per CARI Guidelines (Caring for Australians with Renal Impairment), supplemental iron therapy is recommended for all CRF patients whose serum ferritin is below 100 µg/L or serum transferrin saturation is below 20%.

A lack of response or failure to maintain a haemoglobin response with NESP[a] doses within the recommended dosing range should prompt a search for causative factors. Deficiencies of folic acid or vitamin B12 should be excluded or corrected. Intercurrent infections, inflammatory or malignant processes, osteofibrosis cystica, occult blood loss, haemolysis, severe aluminium toxicity or bone marrow fibrosis may compromise an 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 and bone marrow biopsy demonstrates pure red cell aplasia, testing for anti-erythropoietin antibodies should be conducted.

The safety and efficacy of NESP[a] therapy have not been established in patients with underlying haematologic diseases (e.g. haemolytic anaemia, sickle cell anaemia, thalassaemia and porphyria).

Allergic Reactions
There have been reports of serious allergic reactions including anaphylactic reaction, angioedema, dyspnoea, skin rash and urticaria associated with darbepoetin alfa. Symptoms have recurred with rechallenge, suggesting a causal relationship exists in some cases.

Precautions should be taken when administering NESP[a] in case allergic or other untoward reactions occur. If a serious allergic or anaphylactic reaction occurs, NESP[a] should be immediately discontinued and appropriate therapy administered.

Severe Cutaneous Reactions
Blistering and skin exfoliation reactions including Erythema multiforme and Stevens-Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN), have been reported in a small number of patients treated with darbepoetin alfa in the post-marketing environment. Discontinue darbepoetin alfa therapy immediately if a severe cutaneous reaction, such as SJS / TEN, is suspected. Because severe cutaneous adverse reactions have been seen with other ESAs and are not easily predictable, switching to another ESA is not recommended.

Effects on Fertility
No adverse effects on fertility were observed in male and female rats at IV darbepoetin alfa doses of up to 10 µg/kg 3 times weekly. Systemic exposure (plasma AUC times number of doses/week) at the highest dose was about 4 times greater than that in humans at the recommended initial SC dose of 2.25 µg/kg in cancer patients. An increase in post implantation loss was seen at darbepoetin alfa doses of 0.5 µg/kg/day and higher, but this was considered to be associated with polycythaemia in the dams and is therefore unlikely to be of clinical relevance.

Use in Pregnancy
Pregnancy Category: B3*
*Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Reproductive studies in rats showed no significant placental transfer of darbepoetin alfa. Studies in pregnant rats and rabbits showed no evidence of direct embryotoxic, foetotoxic or teratogenic properties of darbepoetin alfa at IV doses of up to 20 µg/kg/day. Systemic exposure (AUC/dose) at the highest dose was about 4 times (rats) and 20 times (rabbits) that in humans at the recommended initial SC dose of 2.25 µg/kg in cancer patients. Reductions in foetal weights were observed in both species and were probably associated with polycythaemia in the dams. Intravenous injection of darbepoetin alfa to female rats every other day from day 6 of gestation through day 23 of lactation at doses of 2.5 µg/kg/dose and higher resulted in offspring (F1 generation) with decreased body weights, which correlated with a low incidence of deaths, as well as delayed eye opening and delayed preputial separation. No adverse effects were seen in the F2 offspring.

No studies have been conducted in pregnant women. NESP[a] should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation
It is not known whether darbepoetin alfa is excreted in human milk, although many drugs are excreted in human milk. In a reproductive study in rats, IV administration of darbepoetin alfa during gestation and lactation at doses of up to 10 µg/kg/day caused decreases in pup viability during lactation and delays in pup development, in addition to reductions in pup birth weights. Although these effects were probably due to polycythaemia and associated toxicity in the dams, caution should be exercised when NESP[a] is administered to a breastfeeding woman.

Paediatric Use
The safety and efficacy of NESP[a] in paediatric patients have not been established.

Carcinogenicity
Darbepoetin alfa has not been evaluated in standard carcinogenicity bioassays, but there was no evidence from preclinical studies of a proliferative response of any tissue type, other than erythroid progenitor cells, to the drug.

Genotoxicity
Darbepoetin alfa was not mutagenic in assays for gene mutations (bacterial and CHO cell) and was not clastogenic in the mouse micronucleus assay.

Interactions with Other Medicines
The theoretical risk of any drug interaction is low due to the clearance and mechanism of action of NESP[a] (see **PHARMACOLOGY**). No evidence of drug interactions with NESP[a] was observed during the course of clinical studies.

Effects on Laboratory Tests
In clinical studies, no treatment effect was observed for biochemistry parameters. Generally, values remained within the expected range for patients with CRF. Changes in haematology (red blood cells, reticulocytes) were consistent with the pharmacologic effects of darbepoetin alfa.

ADVERSE REACTIONS
Adverse Events in CRF Patients
Data from Clinical Studies
Darbepoetin alfa was well tolerated in clinical studies involving 1578 patients, with an exposure of 942 patient years. The adverse events reported are typical sequelae of CRF and are not necessarily attributable to darbepoetin alfa therapy. The adverse events reported in ≥ 5% of patients treated with darbepoetin alfa compared with r-HuEPO are shown in Table 2. Adverse events reported in < 5% of patients treated with darbepoetin alfa that are considered to be of interest are shown in Table 3. The incidence of deaths was 7% in the darbepoetin alfa-treated patients and 6% in the r-HuEPO-treated patients.

The data described in Table 4 reflect exposure to darbepoetin alfa and placebo in 4,023 patients who received at least one dose of investigational product from the TREAT study, a randomised placebo controlled clinical study in adult CRF patients not on dialysis with type 2 diabetes (see **PRECAUTIONS**).

Table 2 Adverse Events Reported in ≥ 5% of CRF Patients on darbepoetin alfa Compared with r-HuEPO

	Percent of patients reporting events	
Body system and preferred terms	**Darbepoetin alfa n = 1578**	**r-HuEPO n = 591**
Application site		
Injection site pain	7	1
Body as a whole		
Oedema peripheral	10	17
Fatigue	9	11
Fever	9	9
Pain chest	6	9
Access haemorrhage	6	8
Influenza-like symptoms	6	8
Fluid overload	6	8
Access infection	6	6
Cardiovascular		
Hypertension	23	26
Hypotension	22	25
Thrombosis vascular access	8	14
CNS / PNS		
Headache	16	18
Dizziness	8	15
Gastrointestinal		
Diarrhoea	15	21
Vomiting	15	20
Nausea	14	24
Pain abdominal	12	17
Constipation	5	8
Musculoskeletal		
Myalgia	20	27
Arthralgia	11	13
Pain limb	10	16
Pain back	8	12
Respiratory		
Infection upper respiratory	14	23
Dyspnoea	12	18
Cough	10	10
Bronchitis	6	5
Skin and appendages		
Pruritus	8	7

Table 3 Adverse Events of Interest Reported in < 5% of CRF Patients Treated with darbepoetin alfa

	Percent of patients reporting events	
Adverse event	**Darbepoetin alfa n = 1578**	**r-HuEPO n = 591**
CVA / TIA[1]	1	1
Convulsions	1	2
Myocardial infarction	2	2

[1] Cerebrovascular accident / Transient ischaemic attack

Treatment-related events were defined as those occurring in > 0.5% of patients treated with darbepoetin alfa (n=1598) and / or occurring in ≥ 0.2% compared to r-HuEPO (n = 600).

Subject incidence

1 to 10%	Hypertension, injection site pain, headache, thrombosis vascular access
< 1%	Fatigue, anaemia, pruritus, dizziness, hypotension, nausea, arrhythmia, influenza-like symptoms, somnolence, dyspnoea, chest pain, convulsions, abdominal pain, epistaxis.

Thrombotic Events in CRF Patients
Vascular access thrombosis occurred in CRF clinical studies at an annualised rate of 0.19 events per patient year of darbepoetin alfa therapy and 0.40 events per patient year of r-HuEPO. Rates of thrombotic events (e.g., vascular access thrombosis, venous thrombosis and pulmonary emboli) with darbepoetin alfa therapy were similar to those observed in r-HuEPO therapy in these studies.

Table 4 Adverse Reactions Occurring in Adult Patients Not on Dialysis with Type 2 Diabetes (TREAT) with an incidence of ≥ 5% in the darbepoetin alfa group and exceeding the incidence in the placebo group by ≥ 1%.

	Percent of patient adverse reaction reports	
Adverse Reaction	**Darbepoetin alfa Group n = 2004**	**Placebo Group n = 2019**
Hypertension	18%	16%
Renal failure chronic	15%	13%
Urinary tract infection	15%	14%
Hypoglycaemia	14%	13%
Dizziness	12%	10%
Nasopharyngitis	11%	9%
Headache	10%	8%
Fall	8%	7%
Cellulitis	6%	5%
Hypotension	6%	5%
Sinusitis	6%	5%
Contusion	6%	5%
Rash	6%	5%
Skin ulcer	5%	4%
Haematological		
Granulocytopenia	9	7	11
Musculoskeletal		
Pain back	14	16	14
Arthralgia	13	20	6
Pain limb	11	20	7
Myalgia	8	8	5
Pain skeletal	8	12	10
Psychiatric		
Depression	7	8	4
Anxiety	6	9	9
Respiratory		
Dyspnoea	20	20	23
Cough	8	13	13
Infection upper respiratory	8	8	7
Sore throat	6	6	5
Skin and appendages		
Alopecia	8	7	7
Rash	7	9	3

Clinically significant adverse reactions occurring in <1% of cancer patients treated with darbepoetin alfa include: injection site reaction, headache, myalgia, arthralgia and thromboembolic events.

In clinical trials of darbepoetin alfa (n = 873) versus placebo (n = 221), one adverse reaction was reported in ≥ 1% of cancer patients: injection site pain (darbepoetin alfa 4% versus placebo 3%).

Thrombotic Events in Cancer Patients
In cancer patients, the incidence of thrombotic events was 6% for darbepoetin alfa, 5% for r-HuEPO and 4% for placebo. The following events were reported more frequently in darbepoetin alfa-treated patients than in placebo controls, but at a rate comparable to r-HuEPO: pulmonary embolism, thromboembolism, thrombosis and thrombophlebitis (deep and/or superficial).

Adverse Events in Anaemia with Myelodysplastic Syndrome
Adverse reactions including laboratory data abnormalities were reported in 18 (34.6%) of 52 patients including 31 Japanese patients in the safety analysis set of international joint study (phase 2 study). The major adverse reactions were diarrhoea in 2 cases (3.8%), blood alkaline phosphatase increased in 2 cases (3.8%), hyperuricaemia in 2 cases (3.8%), folate deficiency in 2 cases (3.8%), headache in 2 cases (3.8%) and hypertension in 2 cases (3.8%). [Data at the time of approval of additional indication]

Adverse Events, All Patients
Post-marketing Experience
Cases of convulsions have been rarely reported in patients with CRF receiving darbepoetin alfa.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. Radioimmuno-precipitation (RIP) assays were performed on sera from 1534 CRF patients and 833 cancer patients treated with darbepoetin alfa in clinical studies. Antibodies were not detected in the CRF patients; however reactivity, not considered antibody-related was detected in 3 cancer patients. The patients responded to darbepoetin alfa therapy and there was no evidence of PRCA.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Antibody positivity in an assay may also be influenced by sample handling, timing of sample collection, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to darbepoetin alfa with the incidence of antibodies to other products may be misleading.

Rarely, serious allergic reactions have been reported with darbepoetin alfa (see **PRECAUTIONS**).

Severe cutaneous reactions including blistering, skin exfoliation, Erythema multiforme and Stevens-Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN) have been reported in patients treated with darbepoetin alfa. (see **PRECAUTIONS**)

Cases of PRCA associated with neutralising antibodies to erythropoietin have been reported in patients receiving NESP[a] (see **PRECAUTIONS: Pure Red Cell Aplasia**).

DOSAGE AND ADMINISTRATION
For CRF Patients and Patients with Non-Myeloid Malignancies Receiving Chemotherapy
Use the lowest dose of NESP[a] that will gradually increase the haemoglobin concentration to approach a target of not more than 12 g/dL; the rate of haemoglobin increase should not exceed 1 g/dL in any 2-week period.

Rapid increases in haemoglobin concentrations or the use of erythropoietins in subjects with normal haemoglobin concentrations, may result in an increased risk of thrombotic adverse events (see **PRECAUTIONS-Cardiovascular and Thrombotic Events/Increased Mortality**).

CRF Patients
NESP[a] can be administered either SC or IV.

The dose should be started and titrated slowly (e.g. once every 4 weeks) based on individual haemoglobin levels. The haemoglobin target, regardless of the treatment population should not exceed 12 g/dL. (see **Dose Adjustment in CRF patients**). Clinical studies have shown interpatient response to be variable. If a patient fails to respond or maintain a response, other aetiologies should be considered and evaluated (see **PRECAUTIONS: General**). Haemoglobin levels should be monitored frequently until stable. Thereafter, haemoglobin levels can be monitored less frequently. In clinical studies that were used for approval of darbepoetin alfa in patients with chronic renal failure, haemoglobin levels were measured every 1 to 2 weeks.

Dosing instructions are provided for two phases treatment: correction of anaemia and maintenance of the target haemoglobin level. Instructions for dose adjustment and for conversion from recombinant human erythropoietin (r-HuEPO) to NESP[a] are also provided.

Correction of Anaemia
The initial NESP[a] dosage by SC or IV administration is 0.45 µg/kg body weight, as a single injection once weekly. If the increase in haemoglobin is inadequate (less than 1 g/dL in 4 weeks) and iron stores are adequate (see **PRECAUTIONS: General**), the dose of NESP[a] may be increased by approximately 25%. Further increases may be made at 4-week intervals, until the desired response is attained.

Maintenance of Haemoglobin Concentration
In patients on dialysis and not on dialysis, NESP[a] may be dosed weekly or once every 2 weeks at the titrated dose to maintain the target haemoglobin.

If a dose adjustment is required to maintain a target haemoglobin, the individual dose may be adjusted at 4-week intervals until the appropriate haemoglobin level is achieved (see **Dose Adjustment in CRF Patients**).

After any dose adjustment the haemoglobin should be monitored every 1 to 2 weeks until stable and less frequently thereafter. Dose changes in the maintenance phase of treatment should not be made more frequently than every 2 weeks.

When changing the route of administration the same dose should be used and the haemoglobin monitored so that the appropriate NESP[a] dose adjustments can be made to keep the haemoglobin at a target not to exceed 12 g/dL. Data from 809 patients receiving darbepoetin alfa in Australian and 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 IV and SC routes of injection.

Dose Adjustment in CRF Patients
The dose should be adjusted for each patient to achieve and maintain a target haemoglobin not to exceed 12 g/dL. Dose adjustment instructions should be followed to achieve and maintain a target haemoglobin or in response to an excessive rate of rise of haemoglobin.

If the haemoglobin is increasing and approaching 12 g/dL, 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 reinstated at a dose approximately 25% below the previous dose.

If the rise in haemoglobin is more than 1 g/dL in 2 weeks, reduce the dose by 25%.
Haemoglobin levels should be monitored every 1 to 2 weeks until stable and less frequently thereafter.

Conversion from Recombinant Human Erythropoietin to NESP[a]
Due to its longer serum half-life, NESP[a] can be administered less frequently than r-HuEPO. Clinical experience has shown that patients receiving r-HuEPO 2 or 3 times weekly may change to once weekly NESP[a]. Those receiving r-HuEPO once weekly may change to NESP[a] administered once every 2 weeks.

The substitution of NESP[a] for r-HuEPO should be based on the patient's r-HuEPO dose at the time of substitution, and the same route of administration should be used. The initial SC dose of NESP[a] (µg/week) can be determined by dividing the total weekly SC dose of r-HuEPO (U/week) by 200, while the initial IV dose can be determined by dividing the total weekly IV dose of r-HuEPO (U/week) by 240. Because of individual variability, doses should be titrated as described above to maintain the haemoglobin at the desired concentration.

Patients with Non-Myeloid Malignancies Receiving Chemotherapy
Treatment should not be commenced unless haemoglobin falls below 10 – 11 g/dL. The recommended initial dose is 2.25 µg/kg given once weekly as a single SC injection.

The aim of treatment is to increase haemoglobin concentration to a target not to exceed 12 g/dL and to reduce the requirement for blood transfusions. The therapy should be continued for approximately 4 weeks after the end of chemotherapy or until haemoglobin concentrations approach 12 g/dL.

Dose Adjustment-Cancer Patients
If the haemoglobin approaches 12 g/dL, the dose should be reduced by approximately 25% to 50%. If the haemoglobin exceeds 12 g/dL, doses should be temporarily withheld until the haemoglobin decreases to approximately 11 g/dL, at which point therapy should be re-initiated at 25% to 50% below the previous dose.

For patients receiving darbepoetin alfa on a weekly basis if the increase in haemoglobin is inadequate (less than 1 g/dL after approximately 1 month of therapy) or if the response is not satisfactory in terms of reducing red blood cell transfusion requirements, the dose should be doubled to 4.5 µg/kg given once weekly.

Anaemia with Myelodysplastic Syndrome
The usual dose of NESP[a] in adults is 240 µg as darbepoetin alfa (genetical recombination), to be administered as a single subcutaneous injection once weekly. The dose should be decreased in view of the degree of anaemic symptoms and the patient's age.

The efficacy and safety of NESP[a] in combination with other antitumour agents have not been established.

If cases such as excessive haemopoiesis occur (the haemoglobin concentration exceeds approximately 11 g/dL) and dose reduction is required, the dose should be reduced by approximately 50%. If after dose reduction, the haemoglobin concentration falls (below approximately 9 g/dL) and dose increase is required, the dose should be increased approximately twofold. The dose should not exceed 240 µg as a single injection.

If the desired improvement in anaemia is not obtained or anaemia is aggravated after administration of NESP[a], change to another treatment should be considered. The necessity of continued administration of NESP[a] should be assessed at approximately 16 weeks after the initiation of administration. (See **CLINICAL TRIAL**).

Preparation and Administration of NESP[a]
Do not take out the syringe from its pillow package before administration.
Before using NESP[a] Syringe, remove the Tip Cap. Attach an appropriate needle, etc., if necessary, and then administer the drug.
Do not shake NESP[a]. Prolonged vigorous shaking may denature any protein, rendering it biologically inactive.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any products exhibiting particulate matter or discolouration.
Do not dilute or administer NESP[a] in conjunction with other drug solutions.
NESP[a] contains no antimicrobial agent. NESP[a] is for single use in one patient only. Discard any residue.

OVERDOSAGE
The maximum amount of darbepoetin alfa that can be safely administered in single or multiple doses has not been determined. Doses over 3.0 µg/kg/week for up to 29 weeks have been administered to CRF patients without any direct toxic effects of darbepoetin alfa itself. Doses up to 8.0 µg/kg/week and 15.0 µg/kg/3 weeks have been safely administered to cancer patients for up to 22 weeks.
Darbepoetin alfa can result in polycythaemia if the haemoglobin is not carefully monitored and the dose appropriately adjusted. Cases of severe hypertension have been observed following overdose with darbepoetin alfa. If the suggested haemoglobin target range is exceeded, NESP[a] should be reduced or temporarily withheld until the haemoglobin returns to the suggested target range. If withheld, NESP[a] therapy may then be resumed using a lower dose (see **DOSAGE AND ADMINISTRATION**). If clinically indicated, phlebotomy may be performed.

INCOMPATIBILITIES
In the absence of incompatibility studies, NESP[a] should not mixed or administered as an infusion with other medicinal products.

PRESENTATION
NESP[a] is available in the following presentation and packages:
NESP[a] Injection Plastic Syringe 10 µg/0.5 mL 10 syringes
NESP[a] Injection Plastic Syringe 20 µg/0.5 mL 10 syringes
NESP[a] Injection Plastic Syringe 30 µg/0.5 mL 10 syringes
NESP[a] Injection Plastic Syringe 40 µg/0.5 mL 10 syringes
NESP[a] Injection Plastic Syringe 60 µg/0.5 mL 1 syringe
NESP[a] Injection Plastic Syringe 120 µg/0.5 mL 1 syringe
NESP[a] Injection Plastic Syringe 180 µg/0.5 mL 1 syringe
*(*Note: Sterile single-use needles are included. Not all presentations may be available locally.)*

STORAGE
Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light. Do not shake.

Name and Address of Manufacturer
Terumo Corporation, Kofu Factory
1727-1, Tsujiarai, Showa-cho, Nakakoma-gun, Yamanashi, 409-3853, Japan

Name and Address of Product Registrant
Kyowa Kirin Asia Pacific Pte. Ltd.
80 Robinson Road, #22-01
Singapore 068898

Date of HSA Approval: mmm yyyy
Version: 5 (SG) Plastic

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Languge(s):	English		
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