RMYPNPI00

- Long-Acting Erythropoiesis Stimulating Agent -

Biological products, Prescription drug and Prescription drug*
*Caution: Use only as directed by a physician

Storage
Store in a refrigerator container at 2-8 °C and avoid freezing.

Expiration date
Do not use after the expiration date indicated on the package.

Precautions
See PRECAUTIONS FOR HANDLING.

NESP® Injection Plastic Syringe 10 μg / 0.5mL
NESP® Injection Plastic Syringe 20 μg / 0.5mL
NESP® Injection Plastic Syringe 30 μg / 0.5mL
NESP® Injection Plastic Syringe 40 μg / 0.5mL
NESP® Injection Plastic Syringe 60 μg / 0.5mL
NESP® Injection Plastic Syringe 120 μg / 0.5mL
NESP® Injection Plastic Syringe 180 μg / 0.5mL

~ Darbepoetin Alfa (Genetical Recombination) ~

CONTRAINDICATIONS (This product is contraindicated in the following patients.)
Patients with a history of hypersensitivity to any of the ingredients in the product or to other erythropoietic preparations.

DESCRIPTION
One syringe contains the following ingredients.

Brand name	Ingredient/content				Volume in one syringe	pH	Osmotic pressure ratio	Appearance
	Active ingredient		Inactive ingredient					
NESP Injection Plastic Syringe 10 μg / 0.5mL	Darbepoetin Alfa (Genetical Recombination)	10 μg	Polysorbate 80	0.025 mg	0.5 mL	6.0-6.4	About 1 (related to physiological saline)	Colorless and clear solution
NESP Injection Plastic Syringe 20 μg / 0.5mL		20 μg	L-methionine	0.0745 mg				
NESP Injection Plastic Syringe 30 μg / 0.5mL		30 μg	Sodium dihydrogen phosphate dihydrate	1.39 mg				
NESP Injection Plastic Syringe 40 μg / 0.5mL		40 μg	Sodium chloride	4.09 mg				
NESP Injection Plastic Syringe 60 μg / 0.5mL		60 μg	Dibasic sodium phosphate hydrate	q.s.				
NESP Injection Plastic Syringe 120 μg / 0.5mL		120 μg						
NESP Injection Plastic Syringe 180 μg / 0.5mL		180 μg						

*(*Note: Not all preparations may be marketed locally.)*

The active ingredient of this product, Darbepoetin Alfa (Genetical Recombination), is produced in Chinese hamster ovary cells.

<INDICATIONS
NESP is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis.

Anemia with myelodysplastic syndrome.

<<Precautions related to INDICATIONS>
[Anemia with myelodysplastic syndrome]
1. The efficacy and safety of NESP have not been established in patients who are in the intermediate-2- or high risk categories under the IPSS[Note1].
2. Patients indicated for NESP should be selected based on a full knowledge of the description in the "CLINICAL STUDIES" 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.

Note1 International Prognostic Scoring System

DOSAGE AND ADMINISTRATION
[Renal Anemia]
<Hemodialysis patients>
Initial dose
The usual dose of NESP in adult patients is 20 μg as Darbepoetin Alfa (Genetical Recombination), to be administered as a single intravenous injection once weekly.
Initial dose at the switching from erythropoietin preparations (Epoetin Alfa (Genetical Recombination), Epoetin Beta (Genetical Recombination), etc).
The usual dose of NESP in adult patients is 15-60 μg as Darbepoetin Alfa (Genetical Recombination), to be administered as a single intravenous injection once weekly.
Maintenance dose
When correction of anemia is achieved, the usual dose of NESP in adult patients is 15-60 μg as Darbepoetin Alfa (Genetical Recombination), to be administered as a single intravenous injection once weekly. If alleviation of anemia is maintained by once weekly injection, the frequency of administration can be changed to once every two weeks with an initial dose set to be two-fold of the dose in the once weekly injection. In this case, the usual dose in adult patients is 30-120 μg administered as a single intravenous injection once every two weeks.
In all cases, the dose should be adjusted in view of the degree of anemic symptoms and the patient's age, and should not exceed 180 μg as a single injection.

<Peritoneal dialysis patients and patients with chronic kidney disease not on dialysis>
Initial dose
The usual dose of NESP in adult patients is 30 μg as Darbepoetin Alfa (Genetical Recombination), to be administered as a single injection once every two weeks subcutaneously or intravenously.
Initial dose at the switching from erythropoietin preparations (Epoetin Alfa (Genetical Recombination), Epoetin Beta (Genetical Recombination), etc).
The usual dose of NESP in adult patients is 30-120 μg as Darbepoetin Alfa (Genetical Recombination), to be administered as a single injection once every two weeks subcutaneously or intravenously.

Maintenance dose
When correction of anemia is achieved, the usual dose of NESP in adult patients is 30-120 μg as Darbepoetin Alfa (Genetical Recombination), to be administered as a single injection once every two weeks subcutaneously or intravenously.
If alleviation of anemia is maintained by once every two weeks injection, the frequency of administration can be changed to once every four weeks with an initial dose set to be two-fold of the dose in the once every two weeks injection. In this case, the usual dose in adult patients is 60-180 μg administered as a single injection once every four weeks subcutaneously or intravenously.
In all cases, the dose should be adjusted in view of the degree of anemic symptoms and the patient's age, and should not exceed 180 μg as a single injection.

[Anemia with myelodysplastic syndrome]
The usual dose of NESP 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 anemic symptoms and the patient's age.

<Precautions related to Dosage and Administration>
[Renal Anemia]
Regarding the target levels for the improvement of anemia, refer to the guidelines and other relevant updates.
1. Initial dose at the switching from an erythropoietin preparation.
When NESP is started in substitution for an erythropoietin preparation, the dose and the frequency of administration should be determined on the basis of the dose of the erythropoietin preparation that has been used. See the table below.
(1) Patients who have been treated with an erythropoietin preparation twice weekly or three times weekly
Calculate the total dose of the erythropoietin preparation administered during the week before the switching, and then determine the initial dose of NESP according to the table below. The treatment should be started on once weekly basis.
(2) Patients who have been treated with an erythropoietin preparation once weekly or once every two weeks
Calculate the total dose of the erythropoietin preparation administered during the two weeks before the switching, and then determine the initial dose of NESP according to the table below. The treatment should be started on once every two weeks basis.

Total dose of the erythropoietin preparation administered during the week or two weeks before the switching	Dose of NESP
2,000 IU or less	15 μg
4,500 IU	20 μg
6,000 IU	30 μg
9,000 IU	40 μg
12,000 IU	60 μg

2. Dose adjustment
If dose adjustment is required (for example, when the appropriate increase in the hemoglobin concentration or the hematocrit levels cannot be achieved in correction phase, or when the hemoglobin concentration or the hematocrit level deviates from the target range for successive two weeks in maintenance phase), the dose should be increased or decreased according to the table below. Any dose increase should be performed stage by stage in principle.

Table for dose adjustment in the intravenous administration (hemodialysis patients, peritoneal dialysis patients, and patients with chronic kidney disease not on dialysis)

Stage	Dose of NESP
1	15 μg
2	15 μg
3	20 μg
4	30 μg
5	40 μg
6	50 μg
7	60 μg
8	80 μg
9	100 μg
10	120 μg
11	140 μg
12	160 μg
13	180 μg

Table for dose adjustment in the subcutaneous administration (peritoneal dialysis patients and patients with chronic kidney disease not on dialysis)

Stage	Dose of NESP
1	15 μg
2	30 μg
3	60 μg
4	90 μg
5	120 μg
6	180 μg

3. Change of the frequency of administration
(1) When changing the frequency of administration, the hemoglobin concentration or the hematocrit level should be sufficiently monitored before expanding the interval of administration. Be sure that the hemoglobin concentration or the hematocrit level have been kept stable at a certain dose of NESP and then change the frequency of administration from once weekly to once every two weeks, or from once every two weeks to once every four weeks. The hemoglobin concentration or the hematocrit level should be monitored after the change as well, and adjustments should be made as needed.
(2) If the hemoglobin concentration or the hematocrit level fails to reach the target range even with the dose of 180 μg the dose should be reduced by half and the frequency of administration should be changed from once every two weeks to once weekly, or from once every four weeks to once every two weeks.

[Anemia with myelodysplastic syndrome]
1. The efficacy and safety of NESP in combination with other erythropoietic agents have not been established.
2. If cases such as excessive hemoptysis occur (the hemoglobin concentration exceeds approximately 11 g/dL) and dose reduction is required, the dose should be reduced by approximately 50%. If after dose reduction, the hemoglobin 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.
3. If the desired improvement in anemia is not obtained or anemia is aggravated after administration of NESP, change to another treatment should be considered. The necessity of continued administration of NESP should be assessed at approximately 16 weeks after the initiation of administration. (See CLINICAL STUDIES).

PRECAUTIONS
1. Careful Administration (NESP should be administered with care in the following patients.)
(1) Patients with myocardial infarction, pulmonary infarction, cerebral infarction, or those with history of these conditions who may experience thromboembolism [It has been reported that the administration of erythropoietic proteins increased the viscosity of the blood, and may potentially aggravate or induce thromboembolism. Therefore, if NESP is used in these patients, sufficient monitoring is required.]
(2) Patients with hypertension [As the administration of NESP may increase blood pressure and induce hypertensive encephalopathy, sufficient monitoring is required.]
(3) Patients with a history of hypersensitivity to any drug
(4) Patients with an allergic predisposition

2. Important Precautions
[General]
(1) Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), which can be life-threatening or fatal, have been reported in patients treated with hemoglobin concentration set at 11.3 g/dl [1].
3) In patients with renal anemia, type 2 diabetes, and chronic kidney disease who were not on dialysis, even rate of stroke was higher in patients receiving an erythropoiesis stimulating agent targeted to a hemoglobin level of 13 g/dl, than in patients receiving placebo (placebo patients received an erythropoiesis stimulating agent only if their hemoglobin levels were less than 9 g/dL)[2].
(6) When starting NESP or changing the dose of NESP, monitor hemoglobin concentration or hematocrit level, once a week or once every two weeks, until hemoglobin concentration or hematocrit level reach the target range and get stable. If response of excessive hemoptoesis develops, appropriate measures such as temporary discontinuation of NESP should be taken.
(7) Strict administration of NESP may **increase blood pressure** and has been reported to cause **hypertensive encephalopathy**, parameters such as blood pressure, hemoglobin concentration, hematocrit level, etc. should be closely monitored during the treatment. In particular, caution should be exercised to ensure that the hemoglobin concentration or the hematocrit level increases gradually. As NESP is a long-acting drug, its hematopoietic action lasts longer than that of erythropoietin preparations. According to the reports from clinical trials, it took long time for the hemoglobin concentration or the hematocrit level to decrease even after discontinuation of the treatment in some cases. Therefore, patients should be carefully monitored until the hemoglobin concentration or the hematocrit level recovers.
(8) **Pure red cell aplasia** associated with production of anti-erythropoietin antibodies may occur. Its occurrence should be suspected if anemia is not improved or rather exacerbated during the treatment. When pure red cell aplasia is diagnosed, the treatment with NESP should be discontinued and appropriate measures, excluding switching to erythropoietin preparations, should be taken.
(9) Since the administration of NESP may cause hyperkalemia, appropriate dietary control is required.
(10) Iron is an important element for excretion of the pharmacological effect of NESP. Therefore, iron should be administered to patients with iron deficiency.
(11) Since the administration of NESP may cause shunt occlusion or residual blood in hemodialyzers, the flow of blood through shunts and hemodialyzers should be carefully maintained in hemodialysis patients. If such problems occur, appropriate measures, such as reconnecting a shunt or increasing the dose of an anticoagulant, should be taken.
(12) Special attention should be paid to the following patients when the product is used in patients with chronic kidney disease not on dialysis.
1) Body fluid balance is difficult to control in patients with chronic kidney disease not on dialysis. Therefore, closely monitor body fluid and electrolyte balance, renal function, and blood pressure.
2) The effect of this product in improving anemia may

weaken with progress of chronic kidney disease. Serum creatinine concentrations and creatinine clearance must be monitored during treatment with this product, and appropriate measures such as increasing the dose or temporary discontinuation of NESP should be taken.

[Anemia with myelodysplastic syndrome]
(1) NESP should only be administered by or under supervision of a physician with extensive expertise and experience in treating hematologic diseases and only to the patients for whom the use of NESP is considered appropriate.
(2) This product is intended for use in patients who have anemia-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.
(3) 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. In particular, caution should be exercised to ensure that the hemoglobin concentration or the hematocrit level increases gradually. As NESP is a long-acting drug, its hematopoietic action lasts longer than that of erythropoietin preparations. According to the reports from clinical trials, it took long time for the hemoglobin concentration or the hematocrit level to decrease even after discontinuation of the treatment in some cases. Therefore, patients should be carefully monitored until the hemoglobin concentration or the hematocrit level recovers.
(4) During treatment with NESP, the hemoglobin concentration should be carefully monitored at regular intervals. Attention should be paid to prevent excessive hemoptosis (hemoglobin concentration > 11 g/dL). (See CLINICAL STUDIES)
(5) When starting NESP or changing the dose of NESP, measure hemoglobin concentration once a week, until hemoglobin concentration gets stable. If response of excessive hemoptoesis develops, appropriate measures such as temporary discontinuation of NESP should be taken.
(6) Since administration of NESP may **increase blood pressure** and has been reported to cause **hypertensive encephalopathy**, parameters such as blood pressure, hemoglobin concentration, etc. should be closely monitored during the treatment.
(7) **Pure red cell aplasia** associated with production of anti-erythropoietin antibodies may occur. Its occurrence should be suspected if anemia is not improved or rather exacerbated during the treatment. When pure red cell aplasia is diagnosed, the treatment with NESP should be discontinued.
(8) Iron is an important element for excretion of the pharmacological effect of NESP. Therefore, iron should be administered to patients with iron deficiency.

3. Adverse Reactions
[General]
In the post-marketing experience, severe cutaneous reactions including blistering, skin exfoliation, erythema multiforme and SJS/TEN, which can be life-threatening or fatal, have been reported in patients treated with darbepoetin alfa.
[Renal Anemia]
Adverse reactions were reported in 472 (32.3%) of 1462 patients treated with NESP. The major adverse reactions were increased blood pressure in 248 cases (17.0%), shunt thrombosis (occlusion) in 44 cases (3.0%), headache in 29 cases (2.0%) and pruritus in 20 cases (1.4%). [Data at the time of approval of NESP Injection]

[Anemia 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 diarrhea in 2 cases (3.8%), blood alkaline phosphatase increased in 2 cases (3.8%), hypertriglyceridemia 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]

(1) **Clinically significant adverse reactions**
1) **Cerebral infarction (0.8%):** Since cerebral infarction may occur, patients should be closely monitored. If any abnormalities are observed, appropriate measures such as discontinuation of NESP should be taken.
2) **Cerebral hemorrhage (0.4%):** Since cerebral hemorrhage may occur, patients should be closely monitored. If any abnormalities are observed, appropriate measures such as discontinuation of NESP should be taken.
3) **Hepatic function disorder, jaundice (0.1%):** Since hepatic function disorder and/or jaundice accompanied by increased ALT (GPT), γ-GTP, etc. may occur, patients should be closely monitored. If any abnormalities are observed, appropriate measures such as discontinuation of NESP should be taken.
4) **Hypertensive encephalopathy (incidence unknown):** Since hypertensive encephalopathy may occur, patients should be closely monitored for changes in the blood pressure, etc. during the treatment.
5) **Shock and anaphylaxis (incidence unknown):** Since shock and/or anaphylaxis, urticaria, dyspnea, lip edema, pharyngeal edema, etc.) may occur, patients should be closely monitored. If any abnormalities are observed, NESP should be discontinued and appropriate measures should be taken.
6) **Pure red cell aplasia (incidence unknown):** Pure red cell aplasia accompanied by production of anti-erythropoietin antibodies may occur. If such a problem is observed, NESP should be discontinued and appropriate measures should be taken.
7) **Myocardial infarction, pulmonary infarction (incidence unknown):** Since myocardial infarction and/or pulmonary infarction may occur, patients should be closely monitored. If any abnormalities are observed, appropriate measures such as discontinuation of NESP should be taken.

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(2) **Other adverse reactions**

* incidence unknown

	Incidence (%)		
	≥ 1%	1%~ <0.5%	<0.5% or incidence unknown
Cardiovascular	Increased blood pressure (16.7% ≥)	Arrhythmia	Hypotension during dialysis, palpitations, angina pectoris (cardiac muscle ischemia), cerebrovascular obstruction
Dermatologic		Pruritus, rash	
Hepatic	Abnormal hepatic function (Increased ALP, increased γ-GTP, increased AST (GOT), increased ALT (GPT), increased bilirubin)		Cirrhotic polyp
Metabolic			Decreased iron storage, increased serum potassium, increased blood phosphate, increased uric acid, increased cholesterol, secondary hyperuricemia, hyperkalemia
Hematologic		Increased white blood cells, decreased platelets	Increased reticulocyte, decreased lymphocytes, decreased white blood cells
Kidney/urinary		Proteinuria or hematuria (including fluctuation), increased BUN, increased creatinine, etc.	Hematuria
Gastrointestinal			Nausea/vomiting, abdominal pain, gastritis, diarrhoea
Sensory	Headache, tinnitus		Dizziness, insomnia, dysgeusia, extrasensory disorder
Ophthalmologic			Vitreous hemorrhage, conjunctivitis
Others	Blood transfusion reaction, increased CRP		Localized blood in hemodialysis, shortness of breath, pain at the site of shunt, poor hemostasis, diabetic gangrene, fever, muscular skeletal pain, feeling hot/cold flushes, oedema

4. Use in the Elderly

When NESP is used in elderly patients, parameters such as the blood pressure, hemoglobin concentration and hematocrit level should be frequently measured so that the dosage and the frequency of administration can be appropriately adjusted. [The elderly generally have reduced physiological function and are likely to have cardio-vascular complications such as hypertension.]

5. Use during Pregnancy, Delivery or Lactation

(1) Use of NESP in pregnant women or women who may possibly be pregnant is not recommended. When the use is necessary in such women, it should be limited to cases where expected therapeutic benefits outweigh possible risks associated with the treatment. [The safety of NESP in pregnant women has not been established. Growth retardation in fetuses and offspring has been reported in animal studies (using rats and rabbits).]

(2) Use of NESP in lactating women is not recommended. When the use is necessary in such women, the patients should avoid lactation during the treatment. [The safety of NESP in lactating women has not been established. Its transfer to milk has been reported in animal studies (using rats).]

6. Pediatric Use

The safety of NESP in babies with low birthweight, neonates, suckling babies, infants or children has not been established. (NESP has never been used in such patients.)

7. Treatment of Overdosage

During the treatment with NESP, the hemoglobin concentration or the hematocrit level should be carefully monitored at regular intervals to prevent excessive hemoglobin (hemoglobin concentration ≥12 g/dL, or hematocrit level ≥36%). If symptoms of excessive hemoglobin elevation appropriate measures such as temporary discontinuation of NESP should be taken.

8. Precautions Concerning Use

(1) Do not inject NESP with other products.

(2) Before using NESP Syringe, remove the Tip Cap. Attach an appropriate needle, etc., if necessary, and then administer the drug.

(3) Be sure to discard residual solution after use.

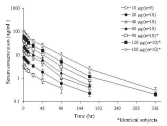
PHARMACOKINETICS

1. Chronic Kidney Disease (Adults)

(1) Single administration [Pk-1)]

1) Intravenous administration

Following a single intravenous administration of NESP at a dose of 16~80 μg to patients with renal anemia receiving hemodialysis, the serum concentration increased almost dose proportionally and its time-course changes showed biphasic elimination. The pharmacokinetic parameters are shown below. AUC also increased almost in proportion to the dose.



Serum concentration-time profiles after a single intravenous administration in hemodialysis patients (Mean ± SD)

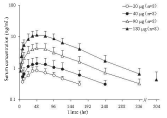
Pharmacokinetic parameters after a single intravenous administration (Mean ± SD)

Dose (μg/m²)	Number of subjects	$t_{1/2}$ (hr)	AUC (μg · hr/mL)	CL (mL/hr/body)	V_{ss} (mL/body)
16	6	21.59~31.40	125.2±23.2	67.45±26.32	2079±618
20	10	34.24±4.62	208.2±38.8	97.21±14.15	3330±589
40	10	32.71±4.44	407.8±3.50	99.13±10.50	3051±454
60	10	32.16±6.53	617.6±133.3	75.17±12.26	3184±560
80	10*	45.27~52.73	1445.9±335.8	54.29±12.22	2667±623
120	10*	48.67±9.62	2675.2±410.9	50.07±11.33	2662±568
180	10*	47.62±6.51	3810.9±496.2	52.86±10.02	2700±545

* Elevated subjects

2) Subcutaneous administration [1)]

Following a single subcutaneous administration of NESP at a dose of 20~180 μg to patients with chronic kidney disease not on dialysis, the serum concentration increased almost dose proportionally. The pharmacokinetic parameters are shown below. AUC also increased almost in proportion to the dose.



Serum concentration-time profiles after a single subcutaneous administration in patients with chronic kidney disease not on dialysis (Mean ± SD)

Pharmacokinetic parameters after a single subcutaneous administration (Mean ± SD)

Dose (μg/m²)	N	$t_{1/2}$ (hr)	C_{max} (ng/mL)	t_{max} (hr)	AUC (ng · hr/mL)
20	8	45.41 ± 21.15	0.882±0.278	48.01 ± 5.5	127.7 ± 4.3
40	8	59.28±24.80	1.721±0.588	52.5±16.9	247.2±104.9
60	8	77.09±31.39	2.356±1.584	56.3±12.7	351.6±262.6
180	8	82.82 ± 16.27	11.64 ± 4.675	52.5 ± 16.1	1675.4 ±600.0

(2) Repeated administration [Pk-1)]

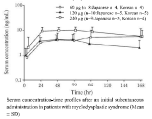
Following repeated intravenous administration of NESP at a dose of 16~40 μg to patients with renal anemia receiving hemodialysis for 28 weeks, no change was found in the pharmacokinetics in the final administration when compared to the initial administration. Following repeated intra-venous administration of NESP at a dose of 80~180 μg to patients with renal anemia receiving dialysis, no major change was found in the serum trough concentration.

Following repeated subcutaneous administration of NESP at a dose of 16~180 μg to patients with peritoneal dialysis and patients with chronic kidney disease not on dialysis, no major change was found in the serum trough concentration.

2. Myelodysplastic syndrome [Pk-2)]

(1) 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 concentration and pharmacokinetic parameters at the initial administration were as follows. C_{max} and AUC$_{168}$ 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/m²)	Number of subjects	C_{max} (ng/mL)	t_{max} (hr)	AUC$_{168}$ (ng · hr/mL)
60	8*	5.04±0.549	42.94±50.18	112.5±51.50
120	10*	5.04±2.271	53.36±52.97	480.8 ±191.2
240	9*	11.23±4.114	50.04±27.42	1589.4±543.3

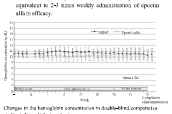
(2) Repeated administration (Japanese and Korean patients)

Following repeated subcutaneous administration of NESP at doses of 60 to 240 μg to patients with myelodysplastic syndromes for 16 weeks, the serum trough concentration was not dose proportional and showed no remarkable changes over the dose range tested throughout the administration period.

CLINICAL STUDIES

1. Double-blind comparative studies (in patients receiving hemodialysis) [E]

NESP or epoetin alfa was intravenously administered to 121 patients with renal anemia receiving hemodialysis (61 patients treated with NESP, 60 patients treated with epoetin alfa) for 28 weeks to examine the equivalence. As a result, once weekly administration of NESP proved to be equivalent to 2~3 times weekly administrations of epoetin alfa in efficacy.



Changes in the hemoglobin concentration in double-blind comparative studies in hemodialysis patients

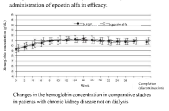
2. Long-term administration studies (in patients receiving hemodialysis) [E]

NESP was (approximately administered to 513 patients with renal anemia receiving hemodialysis at a dose adjusted appropriately in the range of 16~20 μg (1 a frequency of once weekly or once every two weeks for a long-term period. As a result, the hemoglobin concentration remained at around 11.0 g/dL during the treatment in both of the frequencies.

Changes in the hemoglobin concentration in long-term administration studies in patients receiving hemodialysis

3. Comparability studies (in patients with chronic kidney disease not on dialysis) [E]

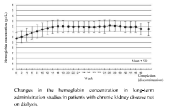
NESP or epoetin alfa were subcutaneously administered to 100 renal anemia patients with chronic kidney disease not on dialysis (50 patients received NESP and 50 patients received epoetin alfa) for 26 ~ 28 weeks to evaluate comparability. As a result, once every two weeks or once every four weeks administration of NESP proved to be equivalent to once weekly or once every two weeks administration of epoetin alfa in efficacy.



Changes in the hemoglobin concentration in comparative studies in patients with chronic kidney disease not on dialysis

4. Long-term administration studies (in patients with chronic kidney disease not on dialysis) [E]

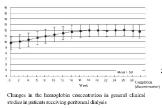
NESP was intermittently administered to 141 renal anemia patients with chronic kidney disease not on dialysis in a frequency of once every two weeks or once every four weeks for 48 ~ 96 weeks. Dose was adjusted in 60, 90, 120 or 180 μg. As a result, after starting administration of NESP, the hemoglobin concentration increased, and after 14 weeks and thereafter the hemoglobin concentration remained at around 12.0 g/dL.



Changes in the hemoglobin concentration in long-term administration studies in patients with chronic kidney disease not on dialysis

5. General clinical studies (in patients receiving peritoneal dialysis) [E]

NESP was intravenously or subcutaneously administered to 146 patients receiving peritoneal dialysis in a frequency of once every two weeks or once every four weeks for 26 ~28 weeks. Dose was adjusted in 30, 60, 90, 120 or 180 μg. As a result, after starting administration of NESP, the hemoglobin concentration increased, and after 14 weeks and thereafter the hemoglobin concentration remained at around 12.0 g/dL.



Changes in the hemoglobin concentration in general clinical studies in patients receiving peritoneal dialysis

6. Multinational clinical study (in patients with myelodysplastic syndromes) [E]

NESP was subcutaneously administered to 52 patients with myelodysplastic syndromes (including 31 Japanese patients) who were in the low or intermediate-1 risk categories under IPSS and transfusion-dependent[*1] with the serum erythropoietin concentration of 500 mIU (international units)/mL or lower at a dose of 60, 120, or 240 μg once weekly for 48 weeks[*2]. The efficacy of NESP was assessed at 16 weeks after the initiation of NESP administration[*2]. In the 50 patients included in efficacy evaluation, major erythroid response[*3] or minor erythroid response[*3] was observed in 11 of 17 patients (64.7%) of the 60 μg group, 8 of 18 patients (44.4%) of the 120 μg group, and 10 of 15 patients (66.7%) of the 240 μg 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 hemoglobin 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 hemoglobin 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, PBSD, MHLW, 2005). To maintain the hemoglobin within the target range of 9.0 to 11.0 g/dL, administration of NESP was suspended if the hemoglobin concentration exceeded 11.0 g/dL.

Note 4) Defined as transfusion independence: first at least 56 consecutive days during the NESP administration period, and the maximum hemoglobin 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.

PHARMACOLOGY

NESP exerts an erythropoietic effect by acting on erythroid progenitor cells directly.[Pd-1)]

1. Erythropoietic Action

When intravenously administered to healthy rats and mice, NESP showed an erythropoietic effect (increasing the hemoglobin concentration and the reticulocyte count) more sustained than that of epoetin alfa. Moreover, when intravenously or subcutaneously administered, to rats with renal anemia, NESP brought about a marked improvement in anemia. In partially nephrectomized rats, NESP showed an effect of improving anemia equivalent to that of epoetin alfa in a lower administration frequency.

2. Mechanism of Action

By binding with erythropoietin receptors, NESP acted on human hematopoietic progenitor cells to overcome colony formation of later erythroid progenitor cells (CFU-E) and early erythroid progenitor cells (BFU-E) in a concentration-dependent manner (*in vitro*).

PHYSICOCHEMISTRY

Nonproprietary name:

Darbepoetin Alfa (Genetical Recombination)

Composition:

NESP is a glycoprotein (molecular weight: ca. 36,000) consisting of 165 amino acid residues ($C_{660}H_{1030}N_{174}O_{198}S_8$, molecular weight: 15,378.59). It is produced in Chinese hamster ovary cells transfected with cDNA of human hepatic cell-derived erythropoietin, which was transformed to change 5 amino acid residues.

PRECAUTIONS FOR HANDLING

1. Do not handle the Plunger Rod forcibly, and do not remove the Black Stop until administration is completed.
2. It is highly recommended that the Syringe should be taken out of the Pillow Bag just before use.
3. Do not use the Syringe, if there is something wrong such as detachment of the Film under the Tip Cap from the tip of the Syringe, or damage of the Syringe, etc.

SHELF LIFE

Shelf-life of the medicinal product : 24 months.

The medicine should not be used after the expiry date (EXP) shown on the pack.

PACKAGING

NESP® Injection Plastic Syringe 10 μg / 0.5mL: 10 syringes
NESP® Injection Plastic Syringe 20 μg / 0.5mL: 10 syringes
NESP® Injection Plastic Syringe 30 μg / 0.5mL: 10 syringes
NESP® Injection Plastic Syringe 40 μg / 0.5mL: 10 syringes
NESP® Injection Plastic Syringe 60 μg / 0.5mL: 1 syringe
NESP® Injection Plastic Syringe 120 μg / 0.5mL: 1 syringe
NESP® Injection Plastic Syringe 180 μg / 0.5mL: 1 syringe
(*Note: Not all presentation may be marketed locally.)

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20) Ito-zone data: Dose response study in patients with myelodysplastic syndrome.

MANUFACTURER:

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Kyowa Kirin Co., Ltd.
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Tokyo, Japan

PRODUCT REGISTRATION HOLDER MALAYSIA:

DKSH MALAYSIA SDN. BHD.
B-2-10, THE ASCENT, PARADIGM
NO.1, JALAN SS7/26A,
KELANA JAYA
47301 PETALING JAYA
MALAYSIA

Date of Revision: September 2024 (Version 6)
RMYPNP/00

SGK KYOWA KIRIN

Packaging Part No. RMYPNP/00
Product Name: NESP
GF number: GF-47900
Artwork Size: 735 x 208 mm
Issued By: SGK
Item Description: 50gsm PI MY
Code: N/A
Method: MY
Language(s): EN
Date Issued: 08-Oct-2024
Revision: 0
No submission only

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Job No. 72006549
Job Name: NESP
Job Number: 68390337
PROOFREADING

Redacted

Version: 00001

SGK is a Mallinckrodt International Corporation

Teckwah Value Chain Pte Ltd

Product Information (INSERT)		Colours	
Customer:	Zuellig Pharma SSG	1C x 1C: Black	
Item:	RMYPNP/00		
Item Description:	In-NESP PI MY		
Material:	50gsm Woodfree		
Open Size:	735mm x 208mm		
Fold Size:	46mm x 104mm		
Changes Required			
Date	**Version**	**Remark**	
27 Nov 2024	V01	Initial Release	
Done By		**Approved By**	
Date	27 Nov 2024	Date	
Name	Huiling	Signature	