Note: This is translated from Japanese package insert of NEUTROGIN®* into English. For the use in other countries, refer to a package insert prepared for each country. *: NEUTROGIN® is the Japanese brand name of GRANOCYTE®.

Revised: Jun 2018 (version 24.0)

Standard Commodity Classification No. of Japan
873399

- RECOMBINANT HUMAN GRANULOCYTE COLONY-STIMULATING FACTOR FORMULATION-

GRANOCYTE® Injection 50 μg
GRANOCYTE® Injection 100 μg
GRANOCYTE® Injection 250 μg

< Lenograstim (Genetical Recombination) formulation >

Biological products,
Prescription drug*1

Storage
Store at room temperature.

Expiration date
Use before the expiration date specified on the package.

Brand name	NEUTROGIN Injection		
	50 μg	100μg	250 μg
Approval No.	20300AMZ00758	20300AMZ00759	20300AMZ00760
Date of listing in the NHI reimbursement price	November 1991	November 1991	November 1991
Date of initial marketing in Japan	December 1991	December 1991	December 1991
Additional indications	September 2000	September 2000	September 2000
Date of latest reexamination	December 2006	December 2006	December 2006

*1: Must be prescribed by a physician or the like

CONTRAINDICATIONS (NEUTROGIN® is contraindicated in the following patients.)

1. Patients with hypersensitivity to this product or any other granulocyte colony-stimulating factor preparations
2. Patients with myeloid leukemia in whom a decrease of blast cells in bone marrow is insufficient and those in whom blast cells are present in peripheral blood. (The count of blast cells may increase.)

DESCRIPTION

In each vial

Trade name		Active Ingredients and contents per vial		Inactive ingredients	Dosage form	Color, appearance	PH*3	Relative Osmotic Pressure*3
NEUTROGIN Injection	50 μg	Lenograstim (Genetical Recombination), JP *2	50 μg	L-arginine 10mg L-phenylalanine 10mg L-methionine 1mg Polysorbate 20 0.1mg D-mannitol 25mg Dilute Hydrochloric Acid q.s.	Lyophilized injection (clear and colorless vial)	A white powder or solid mass	6.0–7.5	Approx. 1
	100 μg		100 μg					Approx. 1
	250 μg		250 μg					Approx. 1-2

Accompanying diluent: Water for injection (JP) 1 mL in each ampoule

*2: This product is produced by usingChinese hamster ovary cell.

*3: After reconstitution with accompanying diluent (relative osmotic pressure in comparison with physiological saline solution)

INDICATIONS, DOSAGE AND ADMINISTRATION

Indications	Dosage and administration (Lenograstim [Genetical Recombination])			
	Time of the start of administration(Time of administration), Route of administration and dosage			Time of discontinuation of administration
Mobilization of Hematopoietic stem cells into peripheral blood	Mobilization after completion of cancer chemotherapy	Adults, Children	The usual dosage for subcutaneous administration is 5 μg/kg once or in two divided doses daily. Dosing should be started the day after the completion of cancer chemotherapy and should be continued until the completion of apheresis. When adequate mobilization effects are not obtained as expected, this product may be administered in doses of up to 10 μg/kg daily. The dosage may be decreased according to the patient's condition.	If the white blood cell count increases to 50,000/mm^3 or more before completion of leukapheresis, the dosage should be decreased. If the white blood cell count reaches 75,000/mm^3 after the dosage is decreased, administration should be discontinued.
	Mobilization induced by this product alone for the purpose of autologous peripheral blood stem cell transplantation	Adults, Children	The usual dosage for subcutaneous administration is 10 μg/kg once or in two divided doses daily for 4 to 6 days until apheresis is completed. The dosage may be decreased according to the patient's condition.	
	Mobilization induced by this product alone in donors of peripheral blood stem cells for transplantation	The usual adult dosage for subcutaneous administration is 10 μg/kg once or in two divided doses daily for 4 to 6 days until apheresis is completed. The dosage may be decreased according to the patient's condition.		

Indications	Dosage and administration (Lenograstim [Genetical Recombination])			
	Time of the start of administration		Route of administration and dosage	Time of discontinuation of administration
Acceleration of the increase in the neutrophil count in hematopoietic stem cells transplantation	Adults	Usually, start dosing on the day after or 5 days after following hematopoietic stem cells transplantation.	i.v. drip infusion of 5 μg/kg once daily	Administration should be discontinued while carefully observing the patient's symptoms when the neutrophil count increases ≥ 5,000 /mm^3.

	Children	Start dosing on day 1 or 5 following hematopoietic stem cells transplantation.			
	Also, when the neutrophil count (a timing indicator for the termination of the administration of the present drug) can not be determined in case of an emergency, it is estimated at half the white blood cell count.				
Cancer chemotherapy -induced neutropenia	Acute myeloid leukemia and acute lympho-cytic leukemia	Adults, Children	Usually, start dosing the day after the completion of cancer chemotherapy in patients in whom the number of blast cells in the bone marrow has decreased sufficiently and blast cells are absent in the peripheral blood.	i.v. injection (including i.v. drip infusion) of 5 μg/kg once daily. If problems such as bleeding tendency do not occur, then administer s.c. injection of 2 μg/kg once daily.	Administration should be discontinued when the neutrophil count reaches 5,000/mm^3 following the neutrophil nadir.

In all cases, adjust the dosage according to the patient's age and symptoms.

Indications	Dosage and administration (Lenograstim [Genetical Recombination])				
	Time of the start of administration			Route of administration and dosage	Time to discontin-ueadministration
Cancer chemotherapy -induced neutropenia	Malignant lympho-ma, small-cell lung cancer, germ cell tumor (testicular cancer, ovarian cancer, etc.), neuroblastoma, and pediatric cancers.	Adults, Children	Usually, start dosing the day after the completion of cancer chemotherapy .	s.c. injection of 2 μg/kg once daily. If subcutaneous injection is difficult due to bleeding tendency, then administer i.v. injection (including drip infusion) of 5 μg/kg once daily.	Administration should be discontinued when the neutrophil count reaches 5,000/mm^3 following the neutrophil nadir.
	Other types of carcinoma	Adults, Children	Usually, start dosing when cancer chemotherapy induces the decrease in the neutrophil count to less than 1,000/mm^3 with a fever (as a general rule, over 38°C) or when it decreases the neutrophil count to less than 500/mm^3. Also, in the case that cancer chemotherapy induces the decrease in the neutrophil count to less than 1,000/mm^3 with a fever (as a general rule, over 38°C) or decreases the neutrophil count to less than 500/mm^3, and that administration of the same chemotherapy is planned consecutively, start dosing when the neutrophil count decreases to less than 1,000/mm^3 in the next course.		
	Also, when the neutrophil count (a timing indicator for the initiation or termination of the administration of the present drug) cannot be determined (e.g., in an emergency), it is estimated at half the white blood cell count.				
Neutropenia in myelodysplas-tic syndrome	Adults	Usually, start dosing when the neutrophil count decreases to < 1,000/mm^3.		i.v. injection of 5 μg/kg once daily	Reduce dosage or discontinue the drug while carefully observing the patient's symptoms when the neutrophil count increases ≥ 5,000/mm^3.
Neutropenia in aplastic anaemia	Adults	Usually, start dosing when the neutrophil count decreases to < 1,000/mm^3.		i.v. injection of 5 μg/kg once daily	
	Children	Start dosing when the neutrophil count decreases to < 1,000/mm^3.		s.c. or i.v. injection of 5 μg/kg once daily	
Congenital or idiopathic neutropenia	Adults	Usually, start dosing when the neutrophil count decreases to < 1,000/mm^3.		s.c. or i.v. injection of 2 μg/kg once daily	
	Children	Start dosing when the neutrophil count decreases to < 1,000/mm^3.			

In all cases, adjust the dosage according to the patient's age and symptoms.

Indications	Dosage and administration (Lenograstim [Genetical Recombination])			
	Time of the start of administration		Route of administra-tion and dosage	Time of discontinuation of administration
Neutropenia that precludes treatment for human immunodeficiency virus (HIV) infection	Adults	Usually, start dosing when the neutrophil count decreases to < 1,000/mm^3.	i.v. injection of 5 μg/kg once daily	The duration of administration is defined as 2 weeks in principle, but the dosage of the drug should be reduced or discontinued when the neutrophil count increases ≥3000/mm^3 while observing the patient's condition.
	Children	Start dosing when the neutrophil count decreases to < 1,000/mm^3.		
Neutropenia in immunosuppres-sive therapy (in kidney transplantation)	Adults	Usually, start dosing when the neutrophil count decreases to < 1,500/mm^3 (WBC < 3,000/mm^3).	s.c. injection of 2 μg/kg once daily	Reduce dosage or discontinue the drug while carefully observing the patient's symptoms when the neutrophil count increases ≥5,000/mm^3.
	Children	Start dosing when the neutrophil count decreases to < 1,500/mm^3 (WBC < 3,000/mm^3).		

In all cases, adjust the dosage according to the patient's age and symptoms.

<Precautions>

○Mobilization of hematopoietic stem cells into peripheral blood

1. If this product is used for patients with cancer for the purpose of autologous peripheral blood stem cell transplantation, the subjects should be limited to patients with malignant tumors sensitive to chemotherapy and/or radiation therapy.

○Cancer chemotherapy-induced neutropenia

1. Ovarian tumors to be diagnosed such as immature teratoma, dysgerminoma, yolk sac tumor, etc. are considered germ cell tumors.
2. The words, "same cancer chemotherapy", in DOSAGE AND ADMINISTRATION for other carcinomas refer to a chemotherapeutic regimen having the same type and dosage of anti-malignant tumor agents as the above cancer chemotherapy.
3. After the administration of this product, when the neutrophil count reaches 5,000/mm^3 following the neutrophil nadir, the use of this product should be discontinued. However, when the neutrophil count recovers to above 2,000/mm^3 and symptoms indicative of infections are absent, thus confirming the safety of the use of this product in patients based on drug reactivity, a reduction of dosage or the termination of drug administration should be considered.

PRECAUTIONS

1. Careful Administration (NEUTROGIN® should be administered with caution in the following patients.)

1) Patients with a history of hypersensitivity to any drugs
2) Patients with a predisposition to allergies
3) Patients with serious hepatic, renal, or cardiopulmonary disorders [Due to insufficient clinical experience, the safety of this product has not yet been established in such cases.]

2. Important Precautions

(1) Precautions for all indications

1) This product should be administered only to patients with neutropenia, or to subjects who must have hematopoietic stem cells mobilized into peripheral blood.
2) During treatment of this product, hematological examinations should periodically be taken to avoid an excessive increase in neutrophil (WBC) count. If an excessive increase in neutrophil (WBC) count is observed, appropriate measures including reducing dosage or discontinuing administration should be taken.
3) Complete medical histories including histories of allergies and drug hypersensitivity should be taken before initiating the therapy with this drug to predict the response of hypersensitivity, etc.

(2) Precautions in the mobilization of hematopoietic stem cells into peripheral blood

1) If this product is administered after completion of cancer chemotherapy to mobilize peripheral blood stem cells, leukapheresis should generally be performed for 1 to 3 days consecutively during convalescence after the patient's white blood cell count has reached its lowest level. The CD34$^+$ cell count in the peripheral blood should be examined.
2) If this product is administered alone to mobilize peripheral blood stem cells, leukapheresis should generally be performed for 1 to 3 days consecutively from the 5th day after start of administration of the drug. The CD34$^+$ cell count in the peripheral blood should be examined.
3) If the collection of peripheral blood stem cells fails when this product is administered to mobilize hematopoietic stem cells into peripheral blood, changes in future treatment schedules should be considered.
4) Luekapheresis should be performed according to appropriate guidelines. Since serious adverse reactions, including cardiac arrest, may develop during leukapheresis, caution should be exercised whenever there are changes in the systemic condition of the patient, including blood pressure. If an adverse reaction occurs, appropriate therapeutic measures should be taken immediately.
5) If peripheral blood stem cells are mobilized using only this product, special attention should be paid to the following, particularly when using this product for donors of peripheral blood stem cells for transplantation.

i) This product should be used for a donor only after full consent has been obtained from the donor or a proxy (if the donor is incapable of giving consent) after the donor and/or proxy have been informed that the long-term safety of the administration of this drug has not been established and that relevant scientific data is still being collected.
ii) When using this product for a donor, tests for HBs antigen, HBc antibody, HCV antibody, HIV-1 antibody, HIV-2 antibody, and HTLV-1 antibody as well as the serological test for syphilis should be performed beforehand to prevent infection of the recipient, and to confirm that there is no risk of infection of the recipient. In addition, serological tests for CMV and herpes virus are also recommended.
iii) When this product is used for a donor, it should generally be administered only to healthy persons in whom no abnormalities were detected during examinations. It is recommended that this product not be administered to patients with splenomegaly, cerebrovascular disorder, ischemic heart disease, thrombosis or autoimmune disease, or a history of these diseases.
iv) Exceeded reaction to this product may cause splenic rupture (refer to (1) Clinically significant adverse reactions of 5) Splenic rupture)).
v) This product should be administered only after confirming that hematological test results are normal, while monitoring the patient's condition. The safety of the patient should also be fully confirmed after the completion of administration of this product.
vi) Since bone pain, fever, headache, malaise, increased Al-P, increased LDH, increased ALT (GPT) and increased AST (GOT) may occur as adverse reactions, this product should be administered with care under careful supervision. The dose and dosing period should be adjusted accordingly.
vii) If bone pain, headaches, and similar symptoms occur after administration of this product, appropriate therapeutic measures should be taken, including the administration of a non-narcotic analgesic. Since thrombocytopenia and other conditions may develop after leukapheresis, drugs for platelet agglutination inhibition (such as aspirin) should be administered with great care.
viii) Since leukopenia or thrombocytopenia may develop after completion of administration of this product or after leukapheresis, changes in hematological test results should be monitored. If severe thrombocytopenia is observed, further leukapheresis should not be performed, and transfusion of platelets of the patient's blood obtained by leukapheresis should be considered.

(3) Precautions regarding neutropenia after cancer chemotherapy, and the acceleration of increase in neutrophil counts during hematopoietic stem cell transplantation

1) Before administering this product to myeloid leukemia patients who have undergone hematopoietic stem cell transplantation, performance of an *in vitro* stimulating test of cell samples is recommended to ascertain whether this product may increase the count of leukemic cells. In addition, perform periodic hematological and bone marrow examinations. If an increase in blast cells is observed, this product should be discontinued.
2) For patients with acute myeloid leukemia, perform periodic hematological and bone marrow examinations. If an increase in blast cells is observed, the administration of this product should be discontinued. Performance of an *in vitro* stimulating test with cell samples is also recommended in advance to ascertain whether this product may increase the count of leukemic cells.
3) For patients with cancer chemotherapy-induced neutropenia, avoid administering this product within 24 hours before and after the administration of cancer chemotherapeutic agents.

(4) Precautions for neutropenia following myelodysplastic syndrome

Since myelodysplastic syndrome associated with increased blast cells carries a risk of becoming myeloid leukemia, performance of an *in vitro* stimulating test with cell samples is recommended in myelodysplastic syndrome patients before starting administration of this product to ascertain that this product does not increase the blast colony.

(5) Precautions for neutropenia that precludes treatment for HIV infections

For patients with neutropenia that precludes treatment for human immunodeficiency virus (HIV) infection, the

duration of administration is, in principle, 2 weeks. Even if further administration is required, the maximum duration is 6 weeks. (The safety of administering this product for longer than 6 weeks has not been established.) Patients should be carefully observed during the period of administration in order to avoid an excessive increase in neutrophils. (Granulocyte precursor cells may decrease, probably leading to diminished response to this product.) If no increase in neutrophil count is observed following a week of treatment, this product should be discontinued and appropriate measures be taken. The underlying disease should be managed carefully, since the possibility that this product may promote the proliferation of HIV cannot be ruled out.

(6) Precautions for neutropenia following immunosuppressive therapy (renal transplantation)

For patients with neutropenia in immunosuppressive therapy (in kidney transplantation), this product should be administered with caution, and the dosage should be adjusted to maintain neutrophils ≥ 2,500/mm^3 (WBC ≥ 5,000/mm^3).

(7) Precautions for congenital neutropenia and neutropenia accompanying aplastic anaemia

If this product is to be self-administered, the patient should be instructed regarding methods of administration and safe disposal.

1) Physicians should carefully consider the appropriateness of self-administration and thoroughly instruct patients. After physician confirm that patients are able to reliably self-administer, self-administration should be conducted under the guidance of a physicians. Instruction should also be provided regarding preparation and administration procedures. Patients should be cautioned to promptly contact their physician if, after use, they suspect an adverse reaction to this product or if continuing self-administration is difficult.
2) Patients should be cautioned not to reuse needles or syringes and should be thoroughly instructed regarding safe disposal methods. When receiving instruction regarding safe disposal of all equipment, patients should ideally be provided with a container in which they can dispose of used needles and syringes.

3. Adverse Drug Reactions

In clinical trials performed before the partial change application (December 2001), adverse reactions were observed in 170 of 1,776 patients (9.6%, 322 reactions). Major adverse reactions were fever in 40 cases (2.3%), back pain 24 cases (1.4%), headache 21 cases (1.2%), bone pain 18 cases (1.0%), increased blast cells (in patients with acute myeloid leukemia) in 17 (1.0%), eruption 10 cases (0.6%), abnormal hepatic function in 7 (0.4%), thrombocytopenia 7 cases (0.4%), malaise 7 cases (0.4%), and chest pain 6 cases (0.4%). Major abnormal changes in laboratory test results were increased LDH in 5.6% (96/1,729), increased Al-P in 5.4% (91/1,696), increased ALT (GPT) in 2.2% (39/1,742), and increased AST (GOT) in 1.4% (24/1,742) of the cases (as of partial change application: December 2001).
In drug use-results surveys performed from the launch of the product up to 1997, adverse reactions were observed in 569 of 6,000 patients evaluated for efficacy (9.5%, 839 reactions). Major adverse reactions were increased LDH in 216 cases (3.6%), increased ALP in 123 cases (2.1%), increased ALT (GPT) in 66 cases (1.1%), fever in 54 cases (0.9%), increased AST (GOT) in 39 cases (0.7%), abnormal hepatic function in 35 cases (0.6%), and back pain in 34 cases (0.6%) (as of reexamination results: September 2006).
In drug use-results surveys performed from 2000 to 2004, adverse reactions were observed in 485 of 1,309 patients (37.1%, 931 reactions) who were evaluated for efficacy (mobilization of hematopoietic stem cells into peripheral blood and acceleration of the increase in the neutrophil count in hematopoietic stem cells transplantation). Major adverse reactions were increased LDH in 333 cases (25.4%), increased ALP in 150 cases (11.5%), back pain in 92 cases (7.0%), fever in 57 cases (4.4%), increased ALT (GPT) in 46 cases (3.5%), increased AST (GOT) in 40 cases (3.1%), and bone pain in 39 cases (3.0%) (as of reexamination results: December 2006).

(1) Clinically significant adverse reactions

1) **Shock and anaphylaxis** (unknown incidence): Since shock and anaphylaxis may occur, patients should be carefully observed. If any abnormalities are observed, this product should be discontinued and appropriate measures be taken.
2) **Interstitial pneumonia** (unknown incidence): Since the development or aggravation of interstitial pneumonia may occur, patients should be carefully observed. If the relevant findings including fever, cough, dyspnea and abnormalities on chest X-ray films appear, this product should be discontinued and appropriate measures taken, such as administering adrenocorticotropic hormone agents.
3) **Increase in blast cells** (unknown incidence): Since this product may promote an increase in blast cells in patients with acute myeloid leukemia and myelodysplastic syndrome, patients should be carefully observed. If an increase in blast cells is observed, this product should be discontinued.
4) **Acute respiratory distress syndrome** (unknown incidence): Since acute respiratory distress syndrome may occur, patients should be carefully observed. If the relevant anomalies including acute progress of dyspnoea, hypoxaemia, and abnormal chest X-ray findings (e.g. bilateral diffuse pulmonary infiltration) are observed, this product should be discontinued and appropriate measures be taken, such as respiratory care.
5) **Splenic rupture** (unknown incidence): If this product is used for a donor or a patient to mobilize hematopoietic stem cells into peripheral blood, excessive reaction to this product may cause splenic rupture. Changes in hematological test results should be monitored, while observing possible effects on the spleen using abdominal ultrasonography. If splenomegaly is observed, appropriate therapeutic measures should be taken, including reducing the dosage or discontinuing administration of this product, according to the patient's condition.
6) **Capillary leak syndrome** (unknown incidence): Since capillary leak syndrome may occur, patients should be carefully observed. If the relevant anomalies including hypotension, hypoalbuminaemia, oedema, pulmonary oedema, pleural effusion, ascites, and haemoconcentration are observed, appropriate measures should be taken, such as discontinuing administration of this product.
7) **Large vessel vasculitis (Inflammation in the aorta, common carotid artery, subclavian artery, or other large vessels)** (unknown incidence): Inflammation in large vessels may occur. If pyrexia, increased C-reactive protein (CRP), aortic wall hypertrophy, or other signs/symptoms are observed, appropriate measures, such as discontinuation of administration, should be taken.

(2) Other adverse reactions

	Unknown incidence	≥2%	<2%
Dermatolo-gic	dermatopathy associated with infiltration of neutrophils, painful erythema, and fever (Sweet syndrome, etc.)		eruption/rash, urticaria, itching
Hepatic			abnormal hepatic function , increased ALT (GPT), increased AST (GOT), increased γ-GTP, increased bilirubin
Gastro intestinal			nausea, vomiting, anorexia, diarrhea, abdominal pain※
Musculo-skeletal	myalgia, pain in extremity		back pain, bone pain, arthralgia, chest pain
Respiratory	pleural effusion		pulmonary oedema, dyspnoea, hypoxaemia
Renal	glomerulonephritis		
Hematolo-gic			thrombocytopenia
Others	palpitations	increased LDH, increased Al-P	fever, increased CRP, increased uric acid, headache, malaise, edema

- The above data are based on the incidences reported in drug use-results surveys that had been performed since the launch of the product up to 2004.
- As to the category marked with※, the data are based on the incidences reported in clinical trials that had been per-

formed up to the partial change application (December 2001).
- With respect to adverse reactions spontaneously reported, the incidence is described as unknown.

4. Use in the Elderly
Frequently monitor the neutrophil (WBC) count, and adjust the administration period as required to avoid an excessive increase in neutrophils (≥ 5,000/mm^3). [Since the elderly are often physiologically hypofunctional, this product should be administered with care.]

5. Use during Pregnancy, Delivery or Lactation
It is advised not to administer to pregnant women or women having possibilities of being pregnant. [The safety of this product has not yet been established in pregnant women.]

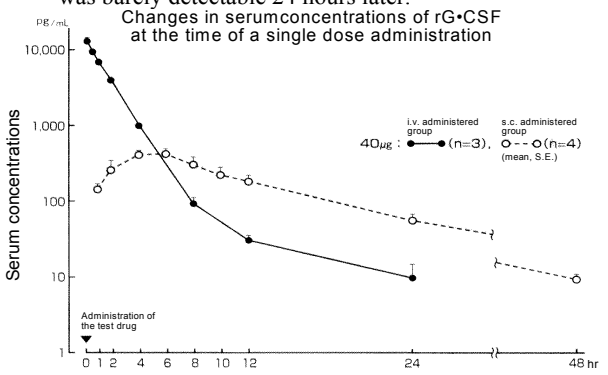
6. Pediatric Use
1) The safety of this product has not been established for prematures, newborns or infants. It is advisable not to administer to such pediatric patients (due to insufficient clinical experience).
2) For pediatric patients, this product should be administered with careful observation.
3) There is insufficient clinical data on child donors of peripheral blood stem cells for transplantation, and the safety of this product has not been established.

7. Precautions concerning use
(1) Preparation of the reconstituted GRANOCYTE solution
1) In using this product, reconstitute the content of 1 vial with the accompanying diluent (1 mL of water for injection, JP).
2) For intravenous drip infusion, mix the reconstituted solution with 5% glucose or physiological saline solution for injection.
(2) Special precautions for disposal and other handling
1) Do not administer this product mixed with other drugs.
2) Discard any unused portion remaining in the vial.
3) The accompanying diluent is supplied as one-point cut ampules. It is advisable that the cut point of the ampule should be wiped with an alcohol swab before opening.
(3) Rate of injection
For intravenous bolus administration, the rate of injection should be as slow as possible.

8. Other Precautions
(1) Among patients with aplastic anaemia and congenital neutropenia who have been treated with granulocyte colony-stimulating factor preparations, transformation to myelodysplastic syndrome or acute myeloid leukemia has been reported.
(2) Among patients with aplastic anaemia, myelodysplastic syndrome and congenital neutropenia who have been treated with granulocyte colony-stimulating factor preparations, the development of chromosomal aberration has been reported.
(3) It has been reported that myeloproliferative disorder and acute myeloid leukaemia occurred in donors of peripheral blood stem cells for transplantation who received a granulocyte colony-stimulating factor preparation.
(4) It has been reported that granulocyte colony-stimulating factors accelerate the proliferation of several types of human bladder cancer cell strains and human osteosarcoma cell strains *in vitro* or *in vivo*.
(5) It has been reported that cerebrovascular disorder, myocardial infarction, cardiac arrest, iritis, gouty arthritis, and non-Hodgkin's lymphoma were observed in donors of peripheral blood stem cells for transplantation who received a granulocyte colony-stimulating factor preparation, though the causal relationship has not been confirmed.

PHARMACOKINETICS

1. Serum Concentration[1)]
(1) Single dose: In a clinical study, lenograstim was intravenously administrated as a single dose of 1, 10, 20 or 40 μg/body[*4] or subcutaneously administrated as a single dose of 10, 20, or 40 μg/body[*4] in healthy male volunteers. In each case the serum concentration values were as follows. In the group receiving subcutaneous administration, serum concentration increased for the first 4–6 hours, and thereafter decreased gradually. In the intravenous administration group, on the other hand, serum concentration was rapidly eliminated after administration, and, 4–8 hours later, serum concentration fell lower than that in the group administered the same dosage subcutaneously. It was barely detectable 24 hours later.



Parameters are presented below.

Route of administration	Dose μg/body [*4]	No. of cases	$t_{1/2}$ h	AUC_{0-72h} pg•h/mL	C_{max} pg/mL
i.v.	1	4	0.43 ± 0.03	476±236	—
	10	3	0.53 ± 0.04	2436±321	—
	20	4	1.02 ± 0.07	9088±484	—
	40	3	1.00 ± 0.05	23325±811	—
s.c.	10	4	5.44 ± 1.89	824±293	89.9 ± 19.7
	20	4	4.49 ± 0.81	1802±610[※2]	151.9 ± 36.9
	40	4	4.39 ± 0.42	6085±890[※2]	478.0 ± 66.1

※2: AUC_{0-96h}

(2) Repeated dose: When this product was intravenously or subcutaneously administered at a dose of 20 μg/body[*4] for 5 consecutive days, serum concentrations on days 1 and 5 showed almost the same elimination pattern, regardless of the route of administration. There were no findings suggesting accumulation of this product.

2. Urinary Excretion[1)]
When this product was administered via i.v. (at a single dose of 1, 10, 20 or 40 μg/body)[*4], via the s.c. route (at a single dose of 10, 20 or 40 μg/body)[*4], and via both i.v. or s.c. routes (at repeated doses of 20 μg/body) [*4]in healthy male volunteers, the urine concentration of this product was undetectable for all routes and dosages.

[*4]: NEUTROGIN is approved for daily doses of 2 to 10 μg/kg (See DOSAGE AND ADMINISTRATION).

CLINICAL DATA

1. Mobilization of hematopoietic stem cells into peripheral blood
Several studies on patients with malignant lymphoma[2)], breast cancer[3,4)], chronic myeloid leukemia[5,6)], and healthy human volunteers[7-9)] have demonstrated that this product induces the mobilization of hematopoietic stem cells that is necessary for the transplantation of peripheral blood stem cells into peripheral blood, regardless of whether the product is administered alone or after cancer chemotherapy.

2. Acceleration of increase of neutrophils in bone marrow transplantation[10)]
A double-blind comparative clinical trial in patients who had undergone bone marrow transplantation revealed that the duration of neutropenia was significantly reduced in the group treated with this product, compared to the control group.

3. Cancer chemotherapy-induced neutropenia
Various clinical trials in cancer patients have shown that this product accelerates recovery from neutropenia caused by cancer chemotherapy. The following cancer types were studied: malignant lymphoma,[11,12)] lung cancer,[13)] acute lymphocytic leukemia,[14-16)] acute myeloid leukemia,[17-20)] urothelial cancer,[21)] head and neck cancer,[22)] breast cancer[23)].

4. Neutropenia in other hematological diseases
Various clinical trials in patients with neutropenic diseases (such as aplastic anaemia[24)], and myelodysplastic syndrome[25)]) showed that this product brought about a rapid increase in neutrophils, and maintained the increased neutrophil count during the administration period.

5. Neutropenia that precludes treatment for human immunodeficiency virus (HIV) infection[26)]
Various clinical trials in patients who had HIV infection, such as acquired immunodeficiency disease syndrome (AIDS) showed that this product produced rapid recovery

and maintenance of the neutrophil count in neutropenic patients who had undergone treatment for HIV infection, and enabled scheduled administration of anti-HIV agents, etc.

6. Neutropenia in immunosuppressive therapy (in kidney transplantation) [27)]

In a double-blind controlled clinical trial in which the patients underwent immunosuppressive therapy after kidney transplantation, this product afforded a rapid recovery and subsequent maintenance of neutrophil count (WBC) in patients with neutropenia (leukocytopenia), and permitted completion of a planned immunosuppressive drug regimen.

PHARMACOLOGY

1. Pharmacological Action

1) This product mobilized and increased hematopoietic stem cells and progenitor cells into peripheral blood in both normal mice and those receiving anticancer agents[28)].
2) Acceleration of neutrophil recovery was observed in various animal models of neutropenia (e.g. cancer chemotherapy-induced neutropenia in mice,[29,30)] BMT mice,[31)] etc.).
3) In cancer chemotherapy-induced neutropenia models (mice), reduced resistance to infection was restored to normal[32)] and augmentation of the therapeutic effect of antibiotics was observed[33)].
Protective action of lenograstim against infections is shown in Table 1. The combined effect of lenograstim and antibiotics in mice is shown in Table 2.

Table 1 Number of surviving mice 7 days following inoculation with P.aeruginosa[32)]

CPA mg/kg i.p.	lenograstim μg/kg s.c	Amount of inoculation (cfu/mice)			
		10^4	10^5	10^6	10^7
0	0	5/5	5/5	5/5	0/5
200	0	3/5	0/5	NT	NT
200	1	5/5	2/5	NT	NT
200	10	5/5	4/5	1/5	NT
200	100	5/5	5/5	2/5	NT

Table 2 Number of surviving mice following inoculation with C. albicans[33)]

CPA mg/kg i.p.	lenograstim μg/kg s.c	AMPH-B mg/kg i.v	Amount of inoculation cfu/mice	Days after inoculation		
				1	2	3
200	0	0	5.1×10^6	0/8	0/8	0/8
200	0	0.5	5.1×10^6	10/10	9/10	0/10
200	100	0.5	5.1×10^6	10/10	10/10	10/10

CPA: cyclophosphamide (JP) AMPH-B: amphotericin B (JP)

4) Lenograstim improved neutropenia resulting from cancer chemotherapy in myeloid leukemia animals (mice) and reduced the duration of neutropenia.[34)]
5) Lenograstim was found not to interfere with the effect of immunosuppressive agents used in organ transplantation in a reaction of mixed lymphocytes using human peripheral blood monocytes (*in vitro*).[35)] It was also found not to interfere with the effect of immunosuppressive agents in a host vs. graft reaction (*in vivo*).[35)]

2. Mechanism of Action

1) Lenograstim is a glycoprotein hematopoietic factor[36,37)] with a structure basically identical to natural human granulocyte colony-stimulating factor. It acts on granulocyte precursor cells in bone marrow, accelerating the differentiation and proliferation of the stem cells toward neutrophils.[38)]
2) When mouse bone marrow cells were cultured in the presence of lenograstim and colony formation ability measured, lenograstim acted on the granulocyte-macrophage colony forming unit (CFU-GM), but did not act on the erythrocyte burst forming unit (BFU-E), the erythrocyte colony forming unit (CFU-E) or megakaryocyte colony forming unit (CFU-Meg) (*in vitro*).[39)]

PHYSICOCHEMISTRY

Nonproprietary name:
Lenograstim (Genetical Recombination) (JAN)

Description:
Genetical recombinated human granulocyte colony-stimulating factor, produced in Chinese hamster ovary cells, A glycoprotein (molecular weight: approx. 20,000) consisting of 174 amino acid residues ($C_{840}H_{1330}N_{222}O_{242}S_8$).

PACKAGING

Injection 50 μg:
Boxes of 1 and 10 vials
Injection 100 μg:
Boxes of 1 and 10 vials
Injection 250 μg:
Boxes of 1 and 10 vials

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