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.)

INDICATIONS, DOSAGE AND ADMINISTRATION

In each vial

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

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

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

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

INDICATIONS, DOSAGE AND ADMINISTRATION

Time of the start of administration (Time of administration), Route of administration and dosage

Mobilization after completion of cancer chemotherapy

- Adults: 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 completion of aplasia. 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.
- 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.

If the white blood cell count increases to 50,000/mm³ or more before completion of leukopheresis, the dosage should be decreased. If the white blood cell count reaches 75,000/mm³ after the dosage is decreased, administration should be discontinued.

Mobilization induced by 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.
- Adolescents, Children: 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.

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/mm³.
In all cases, adjust the dosage according to the patient’s age and symptoms.

### Dosage and administration (Lenograstim [Genetical Recombination])

<table>
<thead>
<tr>
<th>Indications</th>
<th>Time of the start of administration</th>
<th>Route of administration and dosage</th>
<th>Time to discontinuation of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer chemotherapy-induced neutropenia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant lymphoma, small-cell lung cancer, germ cell tumor (testicular cancer, ovarian cancer, etc.), neuroblastoma, and pediatric cancers.</td>
<td>Adults, Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usually, start dosing the day after the completion of cancer chemotherapy in patients whom the number of blast cells in the bone marrow has decreased sufficiently and blast cells are absent in the peripheral blood.</td>
<td></td>
<td>s.c. or i.v. injection of 5 µg/kg once daily.</td>
<td></td>
</tr>
<tr>
<td><strong>Other types of carcinoma</strong></td>
<td>Adults, Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usually, start dosing when cancer chemotherapy induces the decrease in the neutrophil count to less than 1,000/mm³ with a fever (as a general rule, over 38°C) or when it decreases the neutrophil count to less than 500/mm³. Also, in the case that cancer chemotherapy induces the decrease in the neutrophil count to less than 1,000/mm³ with a fever (as a general rule, over 38°C) or decreases the neutrophil count to less than 500/mm³, and that administration of the same chemotherapy is planned consecutively, start dosing when the neutrophil count decreases to less than 1,000/mm³ in the next course.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

### Dosage and administration (Lenograstim [Genetical Recombination])

<table>
<thead>
<tr>
<th>Indications</th>
<th>Time of the start of administration</th>
<th>Route of administration and dosage</th>
<th>Time of discontinuation of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia in myelodysplastic syndrome</td>
<td>Adults</td>
<td>Usually, start dosing when the neutrophil count decreases to &lt;1,000/mm³.</td>
<td>i.v. injection of 5 µg/kg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia in aplastic anaemia</td>
<td>Adults</td>
<td>Usually, start dosing when the neutrophil count decreases to &lt;1,000/mm³.</td>
<td>i.v. injection of 5 µg/kg once daily</td>
</tr>
<tr>
<td>Children</td>
<td>Start dosing when the neutrophil count decreases to &lt;1,000/mm³.</td>
<td>s.c. or i.v. injection of 5 µg/kg once daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Usually, start dosing when the neutrophil count decreases to &lt;1,000/mm³.</td>
<td>s.c. or i.v. injection of 2 µg/kg once daily</td>
<td></td>
</tr>
<tr>
<td>Congenital or idiopathic neutropenia</td>
<td>Adults</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>Start dosing when the neutrophil count decreases to &lt;1,000/mm³.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

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

### Dosage and administration (Lenograstim [Genetical Recombination])

<table>
<thead>
<tr>
<th>Indications</th>
<th>Time of the start of administration</th>
<th>Route of administration and dosage</th>
<th>Time of discontinuation of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia that precludes treatment for human immunodeficiency virus (HIV) infection</td>
<td>Adults</td>
<td>Usually, start dosing when the neutrophil count decreases to &lt;1,000/mm³.</td>
<td>i.v. injection of 5 µg/kg once daily</td>
</tr>
<tr>
<td>Children</td>
<td>Start dosing when the neutrophil count decreases to &lt;1,000/mm³.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia in immunosuppressive therapy (in kidney transplantation)</td>
<td>Adults</td>
<td>Usually, start dosing when the neutrophil count decreases to &lt;1,500/mm³ (WBC &lt;3,000/mm³).</td>
<td>s.c. injection of 2 µg/kg once daily</td>
</tr>
<tr>
<td>Children</td>
<td>Start dosing when the neutrophil count decreases to &lt;1,500/mm³ (WBC &lt;3,000/mm³).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In all cases, adjust the dosage according to the patient’s age and symptoms.
O1. Careful Administration (NEUTROGIN® should be administered with caution in the following patients.)

1) Patients with a history of hypersensitivity to any drug
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.]

O2. Important Precautions

1. (Precautions for all indications)
   - This product should be administered only to patients with neutropemia who must have hematopoietic stem cells mobilized into peripheral blood.
   - During treatment of this product, hematological examinations should periodically be taken to avoid an excessive increase in neutrophil (WBC) count that may occur as adverse reactions, this product should be administered with care under careful supervision. The dose and dosing period should be adjusted accordingly.
   - 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.
   - 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.

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

   i) 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.
   ii) 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.
   iii) 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.
   iv) Leukapheresis 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.
   v) If peripheral blood stem cells 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.
   vi) 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.
   vii) When using this product for a donor, tests for HBs antigen, HBe 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.
   viii) If 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.
   ix) Exceeded reaction to this product may cause splenic rupture (refer to (1) Clinically significant adverse reactions of S) Splenic rupture).

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

   i) 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.
   ii) 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.
   iii) 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/mm³ (WBC ≥5,000/mm³).

(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 confirms that patients are able to reliably self-administer, self-administration should be conducted under the guidance of a physician. 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%), increased LDH in 5.6% (96/1,729), increased Al-P 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 7 (0.4%), thrombocytopenia 7 (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%, 589 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 (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 (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 (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 (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).

(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 in patients who have been 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 be 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 or 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 dyspnea, 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 the 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 haemconcentration are observed, appropriate measures should be taken, such as discontinuing administration of this product.

(2) Other adverse reactions

<table>
<thead>
<tr>
<th>Unknown incidence</th>
<th>&lt;2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>eruption/rash, urticaria, itching</td>
</tr>
<tr>
<td>Hepatic</td>
<td>abnormal hepatic function, increased ALT (GPT), increased AST (GOT), increased γ-GTP, increased bilirubin</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>nausea, vomiting, anorexia, diarrhoea, abdominal pain^</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>back pain, bone pain, arthralgia, chest pain</td>
</tr>
<tr>
<td>Respiratory</td>
<td>pulmonary oedema, dyspnoea, hypoxaemia</td>
</tr>
<tr>
<td>Hematologic</td>
<td>thrombocytopenia</td>
</tr>
<tr>
<td>Others</td>
<td>fever, increased CRP, increased uric acid, headache, malaise, palpitations</td>
</tr>
</tbody>
</table>

^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 performed 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/mm³). (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 leukemia 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 lines 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) Single dose: In a clinical study, lenograstim was intravenously administered as a single dose of 1, 10, 20 or 40 µg/bdy*4 or subcutaneously administered as a single dose of 10, 20, or 40 µg/bdy*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 diminished 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.

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

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 lymphoma2), breast cancer3-4), chronic myeloid leukemia5-6), and healthy human volunteers7-9) 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
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 lymphoma11,12), lung cancer13), acute lymphocytic leukemia14-16), acute myeloid leukemia17-20), urothelial cancer21), head and neck cancer22), breast cancer23).

4. Neutropenia in other hematological diseases
Various clinical trials in patients with neutropenic diseases (such as aplastic anaemia24), and myelodysplastic syndrome25) 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
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) [316]

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, BMT mice, etc.).

3) In cancer chemotherapy-induced neutropenia models (mice), reduced resistance to infection was restored to normal within 1-2 days after injection of the therapeutic effect of antibiotics was observed [35].

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 [35]**

<table>
<thead>
<tr>
<th>CPA (µg/kg i.p.)</th>
<th>lenograstim (µg/kg s.c.)</th>
<th>Amount of inoculation (cfu/mice)</th>
<th>Days after inoculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>5.1 x 10⁶</td>
<td>1</td>
</tr>
<tr>
<td>200</td>
<td>0</td>
<td>5.1 x 10⁶</td>
<td>2</td>
</tr>
<tr>
<td>200</td>
<td>5</td>
<td>5.1 x 10⁶</td>
<td>3</td>
</tr>
<tr>
<td>200</td>
<td>10</td>
<td>5.1 x 10⁶</td>
<td>10/10</td>
</tr>
<tr>
<td>200</td>
<td>100</td>
<td>5.1 x 10⁶</td>
<td>10/10</td>
</tr>
</tbody>
</table>

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.

5) Lenograstim was found not to interfere with the effect of immunosuppressive agents used in organ transplantation 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 erythroid burst forming unit (BFU-E), the erythroid colony forming unit (CFU-E) or megakaryocyte colony forming unit (CFU-Meg) (in vitro) [39].

**PHYSICOCHEMISTRY**

Nonproprietary name: Lenograstim (Genetical Recombination) (JAN)

Description: Genetically 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 (C₅₅₅H₇₁₃O₂₂₂N₂₂₂S₈).

**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

**REFERENCES**


**REQUEST FOR LITERATURE SHOULD BE MADE TO:**

If you would also like to make a request for in-house documents included in the References section, please contact the following.

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