FILGRASTIM MACROLEUCO®

150 mcg / 0.6 mL & 300 mcg / 1.2 mL
Solution For Injection (IV/SC)
Growth Hematopoietic Factor

Filgrastim (Macroleuco®) is a recombinant human granulocyte colony stimulating factor (G-CSF, Filgrastim), which promotes the proliferation and differentiation of neutrophil precursors, the secretion of mature neutrophils from bone marrow, and enhances the function of mature neutrophils. Filgrastim (Macroleuco®) was developed by Dong-A ST Co., Ltd, and is manufactured based on genetic engineering. Filgrastim (Macroleuco®) has been verified for its safety and effect on neutropenia through clinical trials.

Description
Filgrastim (Macroleuco®) is a clear, colorless aqueous solution for parenteral administration.

Formulation
The quantitative composition of Filgrastim (Macroleuco®) is ;

Composition	150 mcg 0,6 mL/vial	300 mcg 1,2 mL/vial
Filgrastim (Host cell : E.coli K-12 W3110 Vector : pCSF451)	150 mcg	300 mcg
Polysorbate 80 (USP)	0,024 mg	0,048mg
Acetic acid (USP)	0,36 mg	0,72mg
Mannitol (USP)	30 mg	60 mg
Sodium hydroxide (USP)	q.s.	q.s.
Water for Injection (USP)	q.s.	q.s.
Ad	0,6mL	1,2 mL

Indications and Usage
Filgrastim (Macroleuco®) is indicated to accelerate the recovery of neutropenia in patients with cancer receiving myelosuppressive chemotherapy and neutropenia in patients with Acute Myelogenous Leukemia receiving induction chemotherapy.

Dosage and Administration
1) Cancer Patients Receiving Myelosuppressive Chemotherapy
In adults and children, the usual dosage for subcutaneous use is 100 ug/m² (adults) and 50 ug/m² (children) of Filgrastim (Macroleuco®) once daily for 10 days.
Administration should start following cancer chemotherapy (on the next day or later). To patients in whose case subcutaneous injection is not appropriate due to a bleeding tendency, etc., 100 ug/m² of Filgrastim (Macroleuco®) should be administered intravenously (including intravenous drip infusion) once daily.
However, administration should be discontinued when the neutrophil count increases to 5,000/mm³ after the period in which the lowest neutrophil count was observed.

2) Patients With Acute Myeloid Leukemia (AML) Receiving Induction Chemotherapy
In adults and children, the usual dosage for intravenous use (including intravenous drip infusion) is 200 ug/m² of Filgrastim (Macroleuco®) once daily.
Administration should start following cancer chemotherapy (on the next day or later) when myeloblasts have sufficiently decreased and are not observed in peripheral blood.
However, administration should be discontinued when the neutrophil count increases to 5,000/mm³ after the period in which the lowest neutrophil count was observed.

Contraindications
1) Patients with known hypersensitivity to any Filgrastim or G-CSF drug.
2) Patients with myeloid leukemia, who show the appearance of promyelocy and myeloblast in peripheral blood.

Warnings
1) Patients with history of drug hypersensitivity.
2) Patients with allergic disposition.
3) Patients with serious hepatic failure, renal failure and cardiopulmonary function.

Adverse Reactions
• **Peripheral Blood Progenitor Cells Mobilization Donors**
Adverse reactions, including abnormalities in laboratory data, to Filgrastim (Macroleuco®) were reported in all 51 patients treated. The most frequently observed adverse reactions included lumbar pain in 24 events (47.1%), headache in 10 events (19.6%), arthralgia in 8 events (15.7%), and fever in 6 events (11.8%). The most frequently observed abnormalities in laboratory data included increased LDH in 44 events (86.3%), increased ALP in 35 events (68.6%), leukopenia/neutropenia in 15 events (29.4%), increased uric acid in 12 events (23.5%), thrombocytopenia in 7 events (13.7%), and increased CRP in 6 events (11.8%).
• **Neutropenia Patients**
Adverse reactions, including abnormalities in laboratory data, to Filgrastim (Macroleuco®) were reported in 679 (10.6%) of 6,391 patients treated. The most frequently observed adverse reactions included skeletal pain (chest, lumbar region, pelvis, etc.) in 97 events (1.5%), fever in 73 events (1.1%), lumbar pain in 52 events (0.8%), and abnormal hepatic function in 39 events (0.6%). The most frequently observed abnormalities in laboratory data included increased LDH in 222 events (3.5%), increased ALP in 202 events (3.2%), increase ALT (GPT) in 68 events (1.1%), and increased AST (GOT) in 51 events (0.8%).
1) Shock : Filgrastim (Macroleuco®) may cause shock. Adequate monitoring should be made. Filgrastim (Macroleuco®) should be discontinued and appropriate therapy instituted when abnormal symptoms are seen.
2) Digestive system : Nausea and vomiting may occur at times. Rarely stomatitis and stomachache may occur.
3) Respiratory system
 1 As Filgrastim (Macroleuco®) may cause the manifestation or exacerbation of interstitial pneumonia, adequate monitoring should be made. Filgrastim (Macroleuco®) should be discontinued and appropriate therapy such as corticosteroid administration instituted if pyrexia, cough, dyspnea, or abnormality in chest X-ray test occur.
 2 As Filgrastim (Macroleuco®) may cause the manifestation of Acute Respiratory Distress Syndrome, adequate monitoring should be made. Filgrastim (Macroleuco®) should be discontinued and appropriate therapy such as breathing care instituted if dyspnea, hypoxia and bilateral obese pulmonary infiltration which are rapidly progressed, or abnormality in chest X-ray test occur.
 3 Sore throat and nasal bleeding may rarely occur.
4) Blood system : In patients with acute myelogenous leukemia and myelodysplastic syndrome, an increase in myeloblasts is observed, administration of the drug should be discontinued. Thrombocytopenia may occur.
5) Splenic rupture may be accompanied with hypersensitivity (anaphylactic) reaction in peripheral blood progenitor cells mobilization donors. Therefore, the donor should be closely monitored by abdominal ultrasound and hematological succession. If a sudden enlargement of the spleen is observed, Filgrastim (Macroleuco®) should be discontinued and appropriate therapy instituted.
6) Dermatological : Skin disorder (Sweet syndrome, etc) which accompanies neutrophil infiltration, painful erythema, fever may occur. Rash, rubor, itch, wheal, and skin trouble may rarely occur.
7) Musculoskeletal system : Ostealgia, lumbago, myalgia may occur at times. Rarely pleurodynia, and arthralgia may occur.
8) Liver : Abnormality in liver, and the transient increase in ALT (GOT) and AST (GPT) may occur.
9) Others : Pyrexia at times (1~5%), increases in LDH, alkaline phosphatase (A1-P), Rarely headache, malaise, palpitation, uric acid and serum creatine, CRP, splenomegaly*, rigid, asthenia, edema, limbs edema, facial edema, pain, neuropathy may occur.
10) The following abnormal reactions, which are not presented in this precaution, are newly reported.,
 Musculoskeletal system : myalgia (5.8%)
 Digestive system : stomatitis (0.4%), stomach-ache (0.6%)
 Body as a whole : rigor (0.9%), asthenia (0.9%), edema (0.3%), the limbs edema (0.1%), facial edema (0.1%), pain (0.4%)
 Nervous system : neuropathy (0.1%)
 Dermatological : itch (0.3%), wheal (0.1%), skin trouble (0.1%)
 Respiratory system : nasal bleeding (0.1%), sore throat

General Precautions
1) Periodic blood tests should be performed during the period of treatment with Filgrastim (Macroleuco®) in order to prevent an excessive increase in neutrophils (WBC).
2) Anaphylaxis, etc., may occur. If such reactions are observed, administration should be discontinued immediately, and appropriate therapy instituted. To assess the risk of hypersensitivity, a careful interview of the patient and a skin reaction test is recommended before administration.
3) Skeletal pain and lumbar pain, etc, may occur after administration of Filgrastim (Macroleuco®). If such symptoms are observed, a non-narcotic analgesic should be administered or other appropriate therapeutic measures should be taken. In case of peripheral blood progenitor cells mobilization donors, a non-narcotic analgesic should be administered or other appropriate therapeutic measures should be taken because there is a high incidence of skeletal pain and lumbar pain, etc. after administration of Filgrastim (Macroleuco®). Since transient thrombocytopenia, etc, associated with the harvesting of peripheral blood progenitor cells may occur, anti-thrombotic drugs such as aspirin should be used with caution.
4) The caution for the increase palpation of neutrophil when transplantation of hematopoietic stem cell, and neutropenia caused by cancer chemotherapy.
 1 For patients with neutropenia caused by cancer chemotherapy, administration of Filgrastim (Macroleuco®) should be avoided 24 hours before and 24 hours after cancer chemotherapy.
 2 In the patients with acute myeloid leukemia (in case of cancer chemotherapy or transplantation of hematopoietic stem cell), the reaction of increase in leukemic cell responding to Filgrastim (Macroleuco®) should be confirmed in vitro prior to Filgrastim (Macroleuco®) treatment.
5) The caution for the administration to neutropenia, which is accompanied with myelodysplastic syndrome.
 It is known that myelodysplastic syndrome accompanied by an increase in myeloblasts may develop into myelogenous leukemia. Therefore, it is recommended to confirm in vitro before administration that there is no evidence of an increase in blast colony formation in collected cells.
6) For patients with acute myelogenous leukemia (treated with cancer chemotherapy and bone marrow transplantation), it is recommended to confirm before administration whether Filgrastim (Macroleuco®) stimulates the proliferation of leukemia cells by conducting an in vitro study using collected cells. Periodic blood tests and bone marrow tests should be performed, and if an increase in myeloblasts is observed, administration of Filgrastim (Macroleuco®) should be discontinued.
7) The caution for the administration to neutropenia conflicting with the treatment of HIV infections. For patients with neutropenia conflicting with the treatment of HIV infections, the treatment period is set at 2 weeks and should not exceed 6 weeks even when continued therapy is required the safety of Filgrastim (Macroleuco®) with a treatment period longer than 6 weeks has not been established.). The product should be administered with care while closely monitoring the patient's condition to prevent an excessive increase in neutrophils (granulocyte precursor cells may be decreased, and the responsiveness to Filgrastim (Macroleuco®) may be reduced.). In cases in which no increase in neutrophil count is observed after the administration of the product for 1 week or longer, administration should be discontinued, and appropriate therapy instituted. Since a possibility of HIV proliferation upon treatment with Filgrastim (Macroleuco®) cannot be ruled out, the primary disease should be carefully monitored.
8) The safety and efficacy have not been evaluated in patients receiving concurrent radiation therapy.
9) Precautions regarding mobilization of hematopoietic progenitor cells to peripheral blood.
 1 In the event that peripheral blood progenitor cells are mobilized from donor, it is recommended to perform properly with referring to the related guidelines. As general malaise, limbs edema, vasovagal reflex, and etc are accompanied with peripheral blood progenitor cells mobilization, the change of general condition such as blood pressure should be monitored,
 2 In the event that Filgrastim (Macroleuco®) is used in donors, the informed consent of the donor or, if incapable of giving consent, the donor's representative, should be obtained prior to administration after fully explaining that the long-term safety of Filgrastim (Macroleuco®) has not been established and that scientific data is currently being collected.
 3 Clinical experience of Filgrastim (Macroleuco®) in donors is limited, Macroleuco® should be administered with care while closely monitoring the condition of the donor after taking donor's general condition into consideration.
 4 In the event that Filgrastim (Macroleuco®) is used in donors, it should be confirmed beforehand that the donor is negative to all of the following tests in order to avoid the transmission of infections to the recipient: HBs antigen, HBc antibody, HCV antibody, HIV-1, -2, and HTLV-I antibodies, and a serological test for syphilis. Serological tests for CMV and herpes should also be performed.
 5 Splenic rupture may occur because of anaphylaxis when administered with Filgrastim (Macroleuco®).
 6 In the event that Filgrastim (Macroleuco®) is used to harvest hematopoietic progenitor cells from autologous peripheral blood progenitor cells following the completion of cancer chemotherapy, the harvest of peripheral blood progenitor cells should be commenced in the recovery period when the WBC increased to 5,000 to 10,000 mm³ after the lowest WBC is observed.
 7 Filgrastim (Macroleuco®) must be administered with caution because thrombocytopenia may occur after administration of Filgrastim (Macroleuco®) and following the harvest of peripheral blood progenitor cells.
 8 Filgrastim (Macroleuco®) must be administered with caution because leukopenia (neutropenia) may occur 1 to 2 weeks after the harvest of peripheral blood progenitor cells.

Pregnancy Category C
The safety of Filgrastim (Macroleuco®) in pregnant women has not been established. Use of Filgrastim (Macroleuco®) in pregnant women or women who may possibly be pregnant is not recommended.

Pediatric Use
1) The safety of Filgrastim (Macroleuco®) in premature infants, neonates, and infants has not been established. Therefore, use of Filgrastim (Macroleuco®) is not recommended (insufficient clinical data).
2) In the event of pediatric use, Filgrastim (Macroleuco®) should be administered with care while closely monitoring the condition of the patients. Clinical experience of Filgrastim (Macroleuco®) in pediatric peripheral blood progenitor cells mobilization donors, in particular, is limited. Therefore, Filgrastim (Macroleuco®) should be administered with care while closely monitoring the condition of the donor after taking the donor's general condition into consideration.

Administration to the elderly
Elderly people generally have weakened physiologic functions, e.g., the function of hematopoiesis, liver, and kidney, so special care should be taken in dosage and administration interval according to each patient's condition.

Precautions in Use
1) Filgrastim (Macroleuco®) should not be administered with the other injection(s) together.
2) When the product is administered intravenously, the injection rate should be as slow as possible.
3) Do not shake.

Other Precautions
1) It has been reported that aplastic anemia and congenital neutropenia in patients treated with G-CSF preparations developed into myelodysplastic syndrome or acute myelogenous leukemia,
2) It has been reported that chromosomal aberration was observed in patients with aplastic anemia, myelodysplastic syndrome, and congenital neutropenia following treatment with G-CSF preparations.
3) It has been reported that myeloproliferative disease or acute myeloid leukemia are developed in the peripheral blood progenitor cells mobilization donors treated with G-CSF.
4) It has been reported that G-CSF preparations showed a facilitatory effect on proliferation of several strains of human bladder cancer and osteosarcoma in vitro or in vivo.
5) In addition to the adverse events described in "Adverse Reactions", temporary cardiac arrest has been reported following the harvest of peripheral blood progenitor cells in peripheral blood progenitor cell mobilization donors treated with G-CSF preparation. However, the relationship with Filgrastim (Macroleuco®) is indefinite. Cardiac failure, vasculitis, cerebrovascular disorder, migraine, diarrhoea, deafness, mediterranean thalassemia, sickle cell crisis, gout, hyperglycaemia, cartilage disorder, ischemic heart disease, myocarditis, amenorrhoea, pulmonary hemorrhage and renal carcinoma have been reported as adverse events.
6) It has been reported that autologous peripheral blood progenitor cells harvested from patients with breast cancer, malignant lymphoma, or myeloma are contaminated with tumor cells.

Caution
Food, Drugs, Devices and Cosmetics Act prohibits dispersing without prescription.

Availability
150 mcg / 0.6 mL - Type I clear & colorless glass vial x 0.6 mL (Box of 10's)
300 mcg / 1.2 mL - Type I clear & colorless glass vial x 1.2 mL (Box of 10's)

Storage
Store at 2℃~ 8℃ Protect from light and heat. Do not shake vigorously. Do not freeze.

FDA Registration No.:
150 mcg / 0.6 mL - BR - 1180
300 mcg / 1.2 mL - BR - 1181
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

First Authorization Date:
150 mcg / 0.6 mL - 22 September 2016
300 mcg / 1.2 mL - 22 September 2016

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