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Summary of Investigation Results

Pegfilgrastim (genetical recombination, including biosimilars)
Filgrastim (genetical recombination, including biosimilars)
Lenograstim (genetical recombination)

October 12, 2023

Non-proprietary name

a., b. Pegfilgrastim (genetical recombination, including biosimilars)

c. Filgrastim (genetical recombination, including biosimilars)

d. Lenograstim (genetical recombination)

Brand name (marketing authorization holder)

See attachment.

Japanese market launch

See attachment.

Indications

See attachment.

Summary of revisions

Precautions concerning myelodysplastic syndrome and acute myeloid leukemia should be added to the IMPORTANT PRECAUTIONS section.

Investigation results and background of the revision

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A retrospective cohort study performed overseas (Adv Ther. 2022; 39: 2778-95, hereinafter referred to as “this study”) suggested an increased risk of myelodysplastic syndrome or acute myeloid leukemia (hereinafter referred to as “MDS/AML”) in patients with breast or lung cancer who were treated with pegfilgrastim (genetical recombination) or filgrastim (genetical recombination) in conjunction with chemotherapy (monotherapy or combination therapy with radiotherapy). Of note, obtaining data on cumulative doses of chemotherapy and radiation therapy was difficult in this study. In addition, as investigational research, it had limitations, such as the possibility that patients treated with granulocyte colony stimulating factor preparations (hereinafter referred to as “G-CSFs”) received higher cumulative doses of chemotherapy and radiotherapy, which are considered to be risk factors for the occurrence of MDS/AML. In contrast to the results of this study, there have been reports in which the use of G-CSFs showed no statistically significant increase in the risk of MDS/AML (Int J Cancer. 2021; 148: 375-84, etc.).

Considering these circumstances, as a result of consultation with expert advisors regarding the necessity of issuing precautions for G-CSFs concerning MDS/AML as well as the contents of precautions, the MHLW/PMDA concluded that revision of PRECAUTIONS for G-CSFs was necessary for the following reasons, although the causal relationship between G-CSFs and MDS/AML was not clear.

- Considering the facts including the use of the outcome definition validated by the previous validation studies, this study was conducted at a certain scientific level, and it suggested an increased risk of MDS/AML from the use of G-CSFs.
- Other than this study, there have been multiple published articles suggesting an increased risk of MDS/AML by the use of G-CSFs in patients receiving chemotherapy (J Natl Cancer Inst. 2007; 99: 196-205, etc.).
- G-CSFs not only promote the proliferation and differentiation of haemopoietic progenitor cells, but also regulate the life of haemopoietic cells through their antiapoptosis effect (Leukemia. 1996; 10: 175-7). There is a report that refers to the possibility that chemotherapy may induce otherwise lethal mutations in myeloid stem cells or progenitor cells, but the antiapoptotic effect of G-CSF saves the mutant cells from destruction, thereby allowing it to develop into a myeloid cancer (N Engl J Med 2006; 354: 2034-45).

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The expert advisors present at the Expert Discussion regarding the current investigation were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the “Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

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Attachment

	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
a.	Pegfilgrastim (genetical recombination)	G-Lasta Subcutaneous Injection 3.6 mg	Kyowa Kirin Co., Ltd.	November, 2014	Prevention of chemotherapy-induced febrile neutropenia, mobilization of haematopoietic stem cells into peripheral blood for allogenic peripheral blood stem cell transplantation
	Pegfilgrastim (genetical recombination, biosimilar 1)	Pegfilgrastim BS Subcutaneous Injection 3.6 mg “Nipro”	Mochida Pharmaceutical Sales Co., Ltd.	Unreleased	Prevention of chemotherapy-induced febrile neutropenia
	Pegfilgrastim (genetical recombination, biosimilar 1)	Pegfilgrastim BS Subcutaneous Injection 3.6 mg “Mochida”	Mochida Pharmaceutical Co., Ltd.	Unreleased	Prevention of chemotherapy-induced febrile neutropenia
b.	Pegfilgrastim (genetical recombination)	G-Lasta Subcutaneous Injection 3.6 mg BodyPod	Kyowa Kirin Co., Ltd.	December 2022	Prevention of chemotherapy-induced febrile neutropenia
c.	Filgrastim (genetical recombination)	Gran Injection 75, 150, M300, Gran Syringe 75, 150, M300	Kyowa Kirin Co., Ltd.	December 1991	Mobilization of haematopoietic stem cells into peripheral blood, promotion of increases in neutrophil count at the time of haematopoietic stem cell transplantation, chemotherapy-induced neutropenia, neutropenia affecting the treatment of human immunodeficiency virus (HIV) infection, neutropenia associated with myelodysplastic syndrome, neutropenia associated with aplastic anaemia, congenital/idiopathic neutropenia, enhancement of the antitumor effect of dinutuximab (genetical recombination) for neuroblastoma, adjunctive therapy with antineoplastic agents for the treatment of relapsed or refractory acute myeloid leukemia

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	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
	Filgrastim (genetical recombination, biosimilar 1)	Filgrastim BS 75 µg Syringe for Inj. Mochida, 150 µg Syringe for Inj. Mochida, 300 µg Syringe for Inj. Mochida	Mochida Pharmaceutical Sales Co., Ltd.	May 2013	Mobilization of haematopoietic stem cells into peripheral blood, promotion of increases in neutrophil count at the time of haematopoietic stem cell transplantation, chemotherapy-induced neutropenia, neutropenia affecting the treatment of human immunodeficiency virus (HIV) infection, neutropenia associated with myelodysplastic syndrome, neutropenia associated with aplastic anaemia, congenital/idiopathic neutropenia
	Filgrastim (genetical recombination, biosimilar 1)	Filgrastim BS Injection Syringe “F” 75 µg, 150 µg, 300 µg	Fuji Pharma Co., Ltd.	May 2013	Mobilization of haematopoietic stem cells into peripheral blood, promotion of increases in neutrophil count at the time of haematopoietic stem cell transplantation, chemotherapy-induced neutropenia, neutropenia affecting the treatment of human immunodeficiency virus (HIV) infection, neutropenia associated with myelodysplastic syndrome, neutropenia associated with aplastic anaemia, congenital/idiopathic neutropenia, adjunctive therapy with antineoplastic agents for the treatment of relapsed or refractory acute myeloid leukemia
	Filgrastim (genetical recombination, biosimilar 2)	Filgrastim BS Injection Syringe “NIG” 75 µg, 150 µg, 300 µg	Nichi-Iko Gifu Plant Co., Ltd.	May 2013	Mobilization of haematopoietic stem cells into peripheral blood, promotion of increases in neutrophil count at the time of haematopoietic stem cell transplantation, chemotherapy-induced neutropenia, neutropenia affecting the treatment of human immunodeficiency virus (HIV) infection, neutropenia associated with myelodysplastic syndrome, neutropenia associated with aplastic anaemia, congenital/idiopathic neutropenia, adjunctive therapy with antineoplastic agents for the treatment of relapsed or refractory acute myeloid leukemia

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	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
	Filgrastim (genetical recombination, biosimilar 2)	Filgrastim BS Injection 75 µg Syringe “NK”, 150 µg Syringe “NK”, 300 µg Syringe “NK”	Nippon Kayaku Co., Ltd.	May 2013	Mobilization of haematopoietic stem cells into peripheral blood, promotion of increases in neutrophil count at the time of haematopoietic stem cell transplantation, chemotherapy-induced neutropenia, neutropenia affecting the treatment of human immunodeficiency virus (HIV) infection, neutropenia associated with myelodysplastic syndrome, neutropenia associated with aplastic anaemia, congenital/idiopathic neutropenia, adjunctive therapy with antineoplastic agents for the treatment of relapsed or refractory acute myeloid leukemia
d.	Lenograstim (genetical recombination)	Neutrogin for Injection 50 µg, 100 µg, 250 µg	Chugai Pharmaceutical Co., Ltd.	December 1991	Mobilization of haematopoietic stem cells into peripheral blood, promotion of increases in neutrophil count at the time of haematopoietic stem cell transplantation, chemotherapy-induced neutropenia, neutropenia associated with myelodysplastic syndrome, neutropenia associated with aplastic anaemia, congenital/idiopathic neutropenia, neutropenia affecting the treatment of human immunodeficiency virus (HIV) infection, neutropenia associated with immunosuppression therapy (renal transplantation), adjunctive therapy with antineoplastic agents for the treatment of relapsed or refractory acute myeloid leukemia