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Summary of Investigation Results

G-CSF preparations

March 31, 2020

Non-proprietary name

a. Nartograstim (genetical recombination)
b. Filgrastim (genetical recombination) and the follow-on biologics (see Attachment)
c. Pegfilgrastim (genetical recombination)
d. Lenograstim (genetical recombination)

Branded name (Marketing authorization holder)

a. Neu-up Inj. 25, 50, 100, 250 (Yakult Honsha Co., Ltd.)
b. Gran Injection 75, 150, M300, Gran Syringe 75, 150, M300 (Kyowa Kirin Co., Ltd.), and the follow-on biologics (see Attachment)
c. G-Lasta Subcutaneous Injection 3.6 mg (Kyowa Kirin Co., Ltd.)
d. Neutrogin Injection 50 μg, 100 μg, 250 μg (Chugai Pharmaceutical Co., Ltd.)

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Indications

a. Promotion of increases in neutrophil count at the time of bone marrow transplantation, treatment of neutropenia caused by cancer chemotherapy, neutropenia associated with pediatric aplastic anemia, congenital/idiopathic neutropenia
b. Mobilization of hematopoietic stem cells to peripheral blood, promotion of increases in neutrophil count at the time of hematopoietic stem cell transplantation, treatment of neutropenia caused by cancer chemotherapy, neutropenia affecting the treatment of human immunodeficiency virus (HIV) infection, neutropenia associated with myelodysplastic syndrome, neutropenia associated with aplastic anemia, congenital/idiopathic neutropenia
c. Prevention of chemotherapy-induced febrile neutropenia
d. Mobilization of hematopoietic stem cells to peripheral blood, promotion of increases in neutrophil count at the time of hematopoietic stem cell transplantation, treatment of neutropenia caused by cancer chemotherapy, neutropenia associated with myelodysplastic syndrome, neutropenia associated with aplastic anemia, congenital/idiopathic neutropenia, neutropenia affecting the treatment of human immunodeficiency virus (HIV) infection, neutropenia associated with immunosuppression therapy (renal transplantation)

Summary of revisions

c. Pegfilgrastim (genetical recombination)

Language concerning an increased risk of thrombocytopenia following administration of this drug identified in an epidemiological study conducted in Japan using a medical information database should be added to the Other Precautions section.

Investigation results and background of the revision

c. Pegfilgrastim (genetical recombination)

Since pegfilgrastim is used on the day following the termination of an antineoplastic agent(s) or later, effects of impaired haematopoiesis caused by the antineoplastic agent(s) could not be excluded. Although the possibility of such effects poses a limitation to the assessment of the association between pegfilgrastim and thrombocytopenia, MHLW/PMDA in consultation with expert advisors and based on the cases involving thrombocytopenia

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reported as follows and the results of the investigation on decreased platelet counts using MID-NET®, concluded that a precaution for thrombocytopenia added to the Other Precautions section was necessary.

■ Reports on adverse reactions

・ Cases involving thrombocytopenia have been reported.

■ Investigation using MID-NET®

1) In the investigation using MID-NET® described in the Appendix, the relative risk (adjusted odds ratio) of decreased platelet counts was statistically significantly increased when pegfilgrastim was prescribed 2 to 7 days before decreased platelet counts occurred compared to no prescriptions of G-CSF preparations. A trend toward an increase in the relative risk of decreased platelet counts was observed when pegfilgrastim was prescribed 8 to 14 days prior to decreased platelet counts.

2) A similar trend to 1) was observed when the observation was limited to 12-week and 16-week periods from the initial antineoplastic prescription in order to eliminate the effects of impaired haematopoiesis that could develop from prolonged use of antineoplastic agents.

3) A similar trend was also observed when the criterion for decreased platelet counts was changed to lower than 25 000/mm^3 (CTCAE v 4.0 Grade 4).

a. Nartograstim (genetical recombination), b. filgrastim (genetical recombination) and d. lenograstim (genetical recombination)

Although the relative risk of decreased platelet counts was statistically significantly increased compared to no prescriptions of G-CSF preparations when each preparation was prescribed the day before decreased platelet counts occurred according to the investigation using MID-NET® described in the Appendix, MHLW/PMDA in consultation with expert advisors concluded that revision of the package insert was not necessary at this time because an effect of an antineoplastic(s) could not be ruled out.

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Number of cases and patient mortalities reported in Japan during the previous 3 fiscal years

Cases involving thrombocytopenia

a. No cases have been reported to date.

b. A total of 4 cases have been reported to date (A causal relationship between the drug and event could not be established for any of these cases.)
No patient mortalities have been reported to date.

c. A total of 30 cases have been reported to date (including 1 case for which a causal relationship between the drug and event could not be ruled out).
No patient mortalities have been reported to date.

d. No cases have been reported to date.

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	Branded name	Marketing authorization holder
b.	Filgrastim (genetical recombination)	Gran Injection 75 Gran Injection 150 Gran Injection M300 Gran Syringe 75 Gran Syringe 150 Gran Syringe M300	Kyowa Kirin Co., Ltd.
	Filgrastim (genetical recombination) and the follow-on biologic 1	Filgrastim BS 75 μg Syringe for Inj. MOCHIDA Filgrastim BS 150 μg Syringe for Inj. MOCHIDA Filgrastim BS 300 μg Syringe for Inj. MOCHIDA	Mochida Pharmaceuticals Co. Ltd.
		Filgrastim BS Injection Syringe 75 μg 「F」 Filgrastim BS Injection Syringe 150 μg 「F」Filgrastim BS Injection Syringe 300 μg「F」	Fuji Pharma Co., Ltd.
	Filgrastim (genetical recombination) and the follow-on biologic 2	Filgrastim BS Inj. 75 μg Syringe 「NK」 Filgrastim BS Inj. 150 μg Syringe 「NK」 Filgrastim BS Inj. 300 μg Syringe 「NK」	Nippon Kayaku Co., Ltd.
		Filgrastim BS Inj. 75 μg Syringe “TEVA” Filgrastim BS Inj. 150 μg Syringe “TEVA”	Teva Takeda Pharma Ltd.

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	Non-proprietary name	Branded name	Marketing authorization holder
		Filgrastim BS Inj. 300 μg Syringe "TEVA"	
	Filgrastim (genetical recombination) and the follow-on biologic 3	Filgrastim BS Inj.75 μg Syringe [SANDOZ] Filgrastim BS Inj. 150 μg Syringe [SANDOZ] Filgrastim BS Inj. 300 μg Syringe [SANDOZ]	Sandoz K.K.

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