Pharmaceuticals and Medical Devices Safety Information

No. 354 July 2018

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Available information is listed here

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Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-8916 Japan

Translated by:
Pharmaceuticals and Medical Devices Agency

Office of Safety I,
Pharmaceuticals and Medical Devices Agency
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-0013 Japan E-mail: safety.info@pmda.go.jp

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Pharmaceuticals and Medical Devices Safety Information

No. 354 July 2018

Ministry of Health, Labour and Welfare & Pharmaceutical Safety and Environmental Health Bureau, Japan

[Outline of Information]

E: Distribution of Dear Healthcare Professional Letters of Emergency Communication *R*: Distribution of Dear Healthcare Professional Letters of Rapid Communications *P*: Revision of Precautions *C*: Case Summaries

Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of providers of medical care and pharmaceutical products.

If providers of medical care and pharmaceutical products such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, it is mandatory for such providers to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As providers of medical care and pharmaceutical products, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADE	Adverse drug event
ADL	Activities of Daily Living
ADR	Adverse drug reaction
BP	Blood pressure
CGA	Comprehensive Geriatric Assessment
CRP	C-reactive protein
FY	Fiscal year
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
MID-NET	Medical Information Database NETwork
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information

1

Guidance of Appropriate Medication for Elderly Patients (general)

1. Introduction

As aged society progresses, safety issues arise more readily in conjunction with polypharmacy (i.e., the concomitant use of multiple drugs) which aims to address symptoms associated with the various age-related physiological changes and co-morbidities. In light of this concern, MHLW established a Study Group on the Appropriate Medication for Elderly Patients (the Study Group) in April 2017 in order to promote safety measures related to drug therapies for geriatric patients, and is currently assessing the factors necessary to ensure safety.

The following paragraphs will introduce the Guidance of Appropriate Medication for Elderly Patients (general) prepared by the Study Group.

2. Guidance of Appropriate Medication for Elderly Patients (general)

(Joint HPB/GAD/MSPO Notification No. 0529-1 and PSEHB/PED Notification No. 0529-1, by the Director of the Office of Medical Safety Promotion, General Affairs Division, Health Policy Bureau, and the Director of the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated May 29, 2018)

[Purpose]

This guidance aims to optimize drug therapies for geriatric patients (avoidance of adverse drug events (ADEs)[1], improvement of medication adherence, avoidance of inadequate medical care) as a summary of fundamental points to consider in order to better administer drug therapies in consideration of the special characteristics of geriatric patients. This guidance is intended to provide reference information to be used in the course of clinical practice and in issuing prescriptions.

This guidance concerns elderly people aged 65 years and older, and places particular focus on patients over the age of 75, a group in which the average number of types of medications used is increased. Additionally, this guidance is aimed primarily at physicians, dentists, and pharmacists, and it is expected that nurses and other occupations will refer to it to aid their understanding of patient medication adherence status and disease symptoms as well as their efforts to support adherence.

[Polypharmacy formation]

The term “polypharmacy” in this guidance denotes not simply using numerous medications concurrently, but rather the various concerns to which this practice can lead, such as increased risk of ADEs, medication errors, decreased medication adherence, among others. There is no strict definition as to how many medications used concurrently will constitute polypharmacy, and the prescriptions best suited to a particular patient may also change in light of her/his overall condition, lifestyle, and living environment.

Typical examples of circumstances where polypharmacy is formed include:

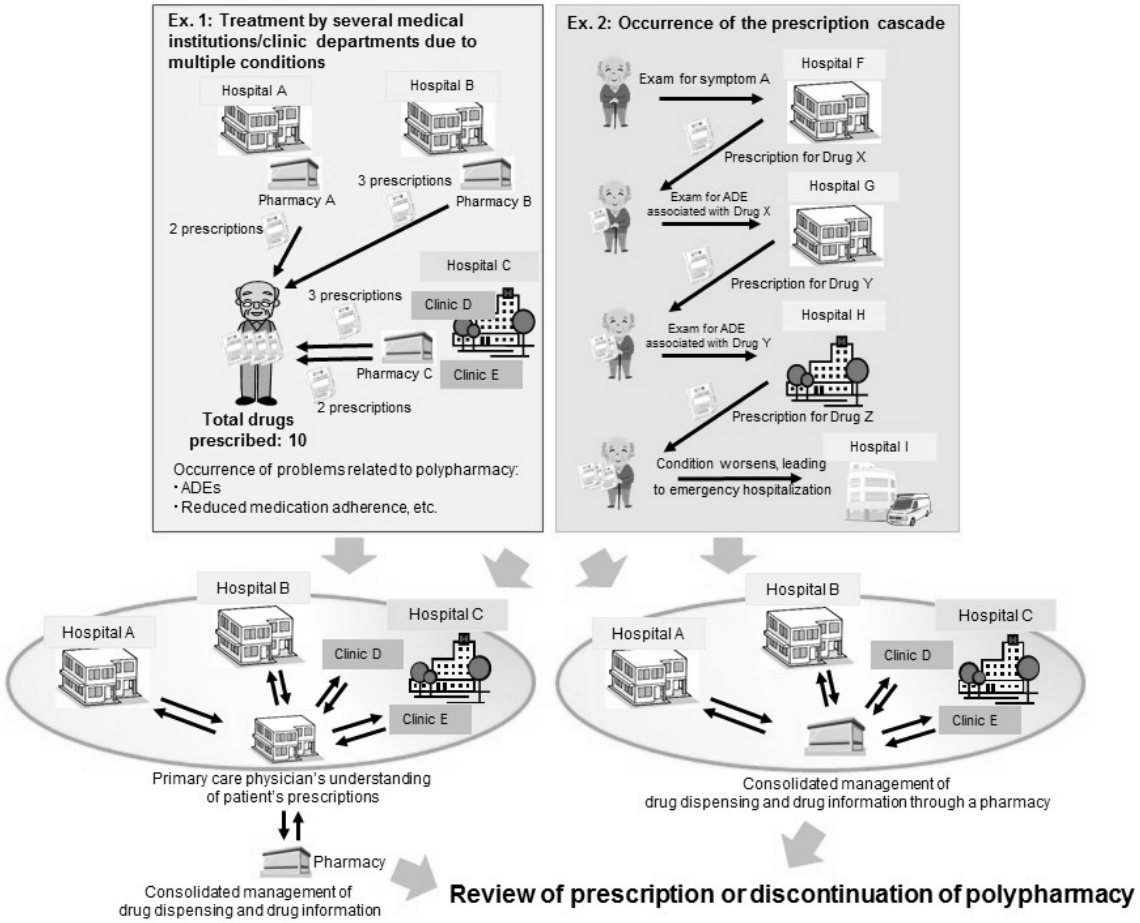
- Cumulative medications as a result of every new hospital or clinic visit due to every new symptoms (Fig. 1, Example 1)
- Occurrence of a “prescription cascade”, where new prescriptions are issued to address ADEs caused by previously prescribed drugs (Fig. 1, Example 2)

Progress towards eliminating polypharmacy arising from such circumstances is expected to be

[1] In this guidance, the term “adverse drug event (ADE)” is used to denote untoward signs or symptoms appearing subsequent to use of drugs whether or not they are caused by such drugs. If a causal relationship with the drugs used is suspected or cannot be ruled out, then the term “adverse drug reaction (ADR)” is used.

achieved as a result of factors such as primary care physicians ensuring they gain a comprehensive understanding of each patient's existing prescriptions when initiating treatment, or through use of a single pharmacy.

Figure 1. Sequence of formation and discontinuation of polypharmacy



[Prescription Review Process]

When considering ways to optimize a patient's treatment regimen, it is necessary to sufficiently understand the patient's current diseases, any co-morbidities such as geriatric syndromes, her/his Activities of Daily Living (ADL), living environment, as well as all available information concerning medications currently used by her/him, and use of the Comprehensive Geriatric Assessment (CGA) is recommended (Fig. 2-1). With evaluating the efficacy and safety of the patient's whole prescription medicines, whether problems stemming from polypharmacy are actually occurring should be confirmed. If there are such problems, the decision to continue the patient's current regimen or implement necessary adjustments should be made by following the flowchart provided in Fig. 2-2.

Figure 2-1. Prescription review process

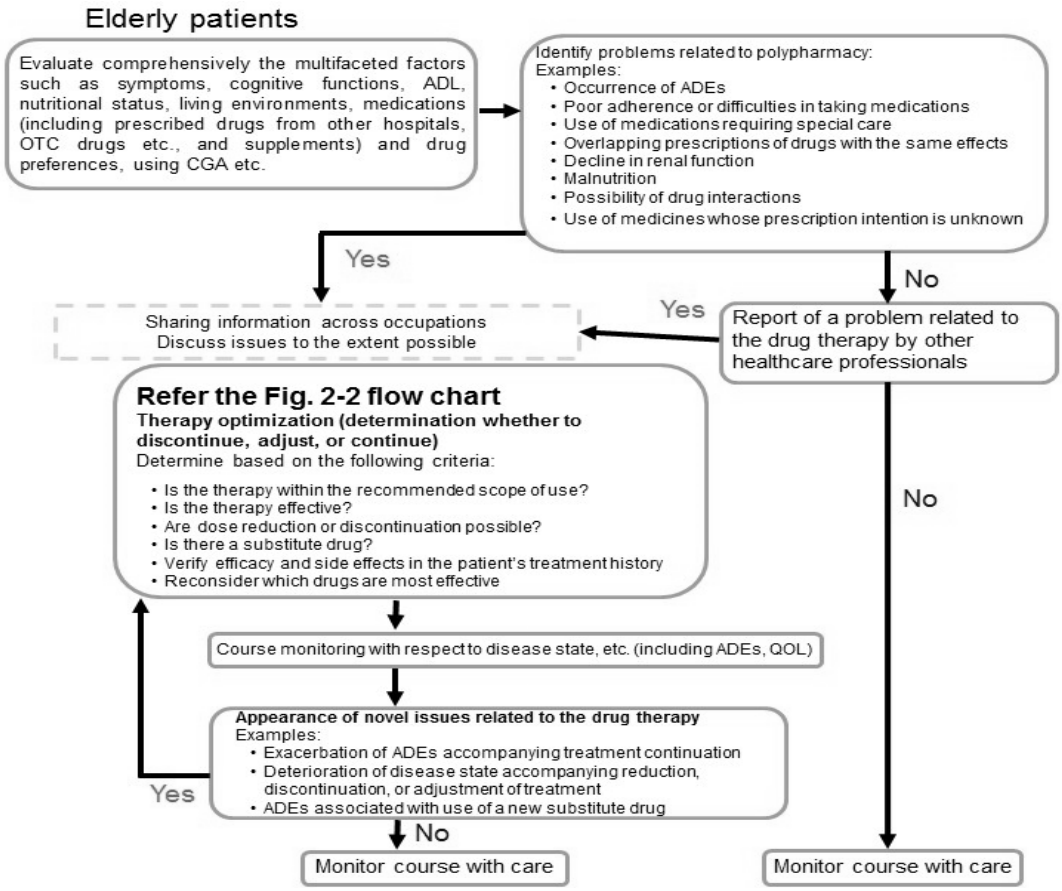
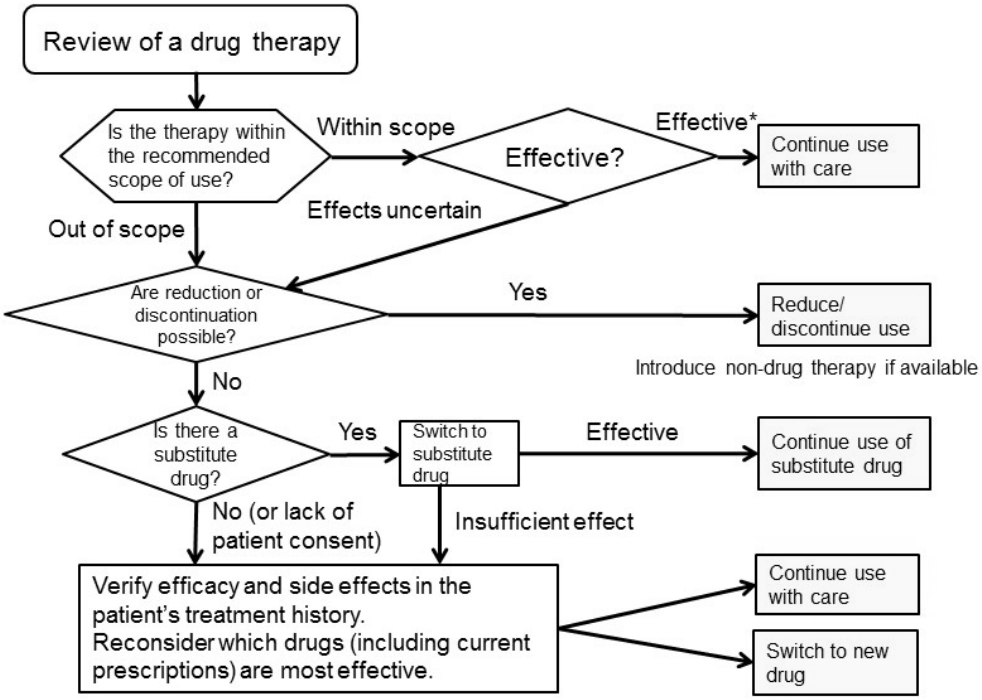


Figure 2-2. Flow chart for optimizing a patient's drug therapy regimen



*When considering prophylactic use, make decisions based on the expected effect and necessity of drugs

(Excerpted from the "Guidelines for Medical Treatment and its Safety in the Elderly 2015" (The

Japan Geriatrics Society))

[Items to consider as countermeasures against polypharmacy related to the administration of drugs to geriatric patients]

Regarding drugs frequently used by the elderly and their drug interactions, basic items to consider are summarized in terms of selecting treatments, dosages, and dosing forms accommodating the characteristics of geriatric patients, as well as possible interactions with drugs from other classes, based on characteristics of each drug. (Table 1: Guidance of Appropriate Medication for Elderly Patients (general) excerpted from the Appendix).

Table 1. Fundamental points to consider regarding drugs frequently used by geriatric patients

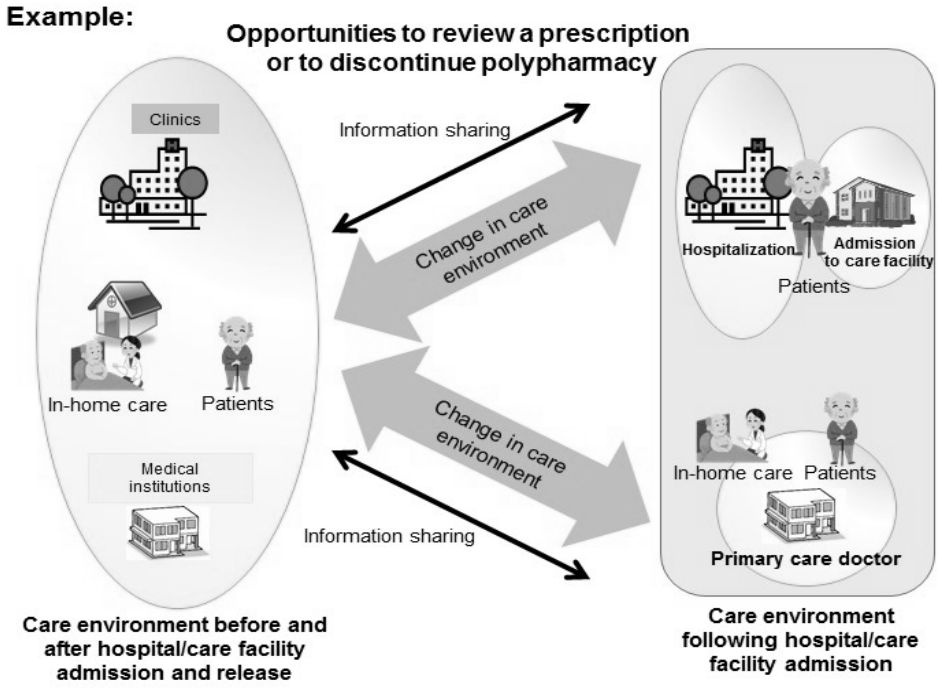
(Drug classes and non-proprietary names of representative drugs [Examples of branded names])

A. Hypnotics-sedatives/ anxiolytics	**Lifestyle instructions related to sleeping habits should be provided before prescribing drug therapy in light of the fact that sleeping time and quality are reduced as a result of aging. While use of hypnotics-sedatives or anxiolytics may be used as necessary, benzodiazepines have been identified as a drug class requiring particularly careful administration due to the likelihood of adverse events in geriatric patients associated with their use as well as their potential to formulate dependence.**	
	Drug selection accounting for geriatric patient characteristics	Use of **benzodiazepine-class hypnotics-sedatives (e.g., brotizolam [Lendormin], flunitrazepam [Rohypnol, Silece], nitrazepam [Benzalin, Nelbon], etc.)** is associated with a greater risk of oversedation, deterioration of cognitive function, deterioration of motor functions, fall, bone fractures, or delirium. As such, special care is required when these drugs are prescribed to geriatric patients. **Long-acting benzodiazepines (e.g., flurazepam [Dalmate], diazepam [Cercine, Horizon], haloxazolam [Somelin], etc.)** should not be prescribed to geriatric patients because such patients commonly exhibit reduced metabolism of benzodiazepines as well as increased sensitivity. Additionally, **triazolam [Halcion]** carries a risk of causing amnesia and should refrain from its use as much as possible. An increased risk of falls and fractures has also been reported with respect to **non-benzodiazepine hypnotics-sedatives (e.g., zopiclone [Amoban], zolpidem [Myslee], eszopiclone [Lunesta], etc.)**. Other adverse events similar to those associated with benzodiazepine use may also appear. **Benzodiazepine-class anxiolytics (e.g., alprazolam [Constan, Solanax], etizolam [Depas] etc.)** may be used to address anxiety and irritation occurring during the day. However, elderly people are at greater risk of developing the aforementioned adverse events and should refrain from their use as much as possible.

[Timing of prescription review]

The general expectation concerning the review of prescriptions is that review will be done at every opportunity in conjunction with monitoring of the patient's medical condition during the acute and chronic phases of disease. Particularly apt opportunities for reconsidering prescriptions include occasions when there is a change in the patient's care environment, such as hospital release/transfer, admission/relocation to a nursing-care facility, introduction to home-based medical care, or initiation of new treatment by a primary care physician. When a change in the patient's care environment is expected, prescriptions must be reviewed assuming a continued management of the patient in the new environment (Fig. 3).

Figure 3. Diagram of prescription revision accompanying changes in care environment



[Support of medication adherence]

Medication adherence by geriatric patients often decreases along with complications caused by increased number of prescribed drugs and their ailing capacity to manage their medications. Support must be given to those patients to properly use their medications based on the understanding of the factors causing their medication adherence to decrease and subsequent accurate assessment of their capacity to manage their medications. Examples are given as ways to increase medication adherence and medication support, with regard to “reducing the number of drugs”, “dosage form selection”, “simplification of use”, “considering suitable formulations”, “considering a suitable management method”, and “consolidated management of prescription and dispensing”.

[Multi-occupational/institutional, and community cooperation]

Collaboration across multiple or within the same occupations is important in various situations involving drug therapy. In particular, physicians, dentists, and pharmacists are required to play a central role in drug therapy. In addition, nurses, for example, are generally expected to collect information on patients’ adherence, their ability to manage their medications, and their symptoms suspected to indicate ADEs in the course of medication adherence support, and to share the information across multiple occupations.

When a patient is to be admitted or released from a hospital, cooperation with that patient’s primary care physician is necessary beforehand and afterward in order to confirm the rationales behind the patient’s prescriptions and any post-release policy. Hospital pharmacists are also expected to provide information on prescription medications and other relevant information to the pharmacists of the local pharmacies as well as other medical personnel associated with the community-based integrated care system to be used after release. Ensuring the sufficient provision of prescription information from community pharmacists to hospital pharmacists is also necessary for a bilateral information sharing.

In addition, it is necessary to provide information to enable physicians to review prescriptions in nursing care facilities, or home medical care and outpatient settings in cooperation with related parties across various occupations as part of the community-based integrated care system.

[Fostering public understanding]

In order for this guidance to gain broad adoption in the medical community, it is necessary to

promote understanding by the general population, which includes patients receiving medical care and their families. Although it may be difficult for patients, families, and care workers to understand the concerns associated with polypharmacy and the necessity of providing appropriate medication adherence support, each of these groups must understand that reducing the dosage or discontinuing a specific treatment in some cases can result in improvement, and knowledge of the proper uses of drugs should also be disseminated widely among the public.

3. To conclude

The Study Group plans to prepare in the future specific considerations based on the characteristics of different patients' care environments, as supplements to this guidance. As the details of the substantive considerations comprising each discussion will be made public on the MHLW website, please refer to the relevant webpage to review further information concerning the current status of the Study Group's investigation.

As this guidance was prepared with the intent of supporting the application of improved practices for administering drug therapy that incorporate considerations of the characteristics of geriatric patients, we encourage healthcare professionals to use it as a reference. In addition, to mitigate problems related to polypharmacy, it is essential to first foster the understanding by the general population, which includes patients receiving medical care and their family members. We request the support and cooperation of healthcare providers in continuing their ongoing educational activities in order to help disseminate information concerning the appropriate uses of medicines throughout the general public.

4. Reference Information

- Study Group on the Appropriate Medication for Elderly Patients
  http://www.mhlw.go.jp/stf/shingi/other-iyaku.html?tid=431862 (only in Japanese)

- Working Group for the Creation of Guidelines of Appropriate Medicaton for Elderly Patients
  http://www.mhlw.go.jp/stf/shingi/other-iyaku.html?tid=475677 (only in Japanese)

- Guidance of Appropriate Medication for Elderly Patients (general)
  Joint HPB/GAD/MSPO Notification No. 0529-1 and PSEHB/PED Notification No. 0529-1, by the Director of the Office of Medical Safety Promotion, General Affairs Division, Health Policy Bureau, and the Director of the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated May 29, 2018
  http://www.mhlw.go.jp/file/05-Shingikai-11121000-Iyakushokuhinkyoku-Soumuka/0000209384.pdf (only in Japanese)

2

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated June 5, 2018, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 [1] Pegfilgrastim (genetical recombination)
[2] Filgrastim (genetical recombination, including follow-on biologics)
[3] Lenograstim (genetical recombination)

Branded name (name of company)	[1] G-Lasta Subcutaneous Injection 3.6 mg (Kyowa Hakko Kirin Co., Ltd.) [2] Gran Injection 75, 150, Gran Injection M300, Gran Syringe 75, 150, Gran Syringe M300 (Kyowa Hakko Kirin Co., Ltd.) and the other follow-on biologics [3] Neutrogin Injection 50 μg, 100 μg, 250 μg (Chugai Pharmaceutical Co., Ltd.)
Therapeutic category	Blood and body fluid agents-Miscellaneous
Indications	[1] Pegfilgrastim (genetical recombination) • Prevention of chemotherapy-induced febrile neutropenia [2] Filgrastim (genetical recombination, including follow-on biologics) • 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 which affecting the treatment of human immunodeficiency virus (HIV) infection • Neutropenia associated with myelodysplastic syndrome • Neutropenia associated with aplastic anemia • Congenital/idiopathic neutropenia [3] Lenograstim (genetical recombination) • 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 which affecting the treatment of human immunodeficiency virus (HIV) infection • Neutropenia associated with immunosuppressive treatment (renal transplant)

PRECAUTIONS (revised language is underlined)

Adverse reactions (clinically significant adverse reactions)

Large vessel vasculitis (Inflammation in the aorta, common carotid artery, subclavian artery, or other large vessels):
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.

Reference information

Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported in approximately the previous 2 years and 11 months (April 2015 to March 2018).
Cases involving large vessel vasculitis:
[1] Pegfilgrastim (genetical recombination):
11 cases (no patient mortalities)
[2] Filgrastim (genetical recombination, including follow-on biologics):
1 cases (no patient mortalities)
[3] Lenograstim (genetical recombination)
2 cases (no patient mortalities)

Number of patients using the drug as estimated by the MAH during the previous 1-year period: [1] approximately 47 000
[2] approximately 30 000 [3] approximately 12 000

Launched in Japan: [1] November 2014 [2] December 1991
[3] December 1991

Pegfilgrastim case summary

No.	Patient		Daily dose/Treatment duration	Adverse reactions	
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 60s	Neutropenia (gastrooesophageal reflux disease)	3.6 mg Once	**Aortitis**	
				126 days before administration	The patient was diagnosed with right breast cancer.
				98 days to 28 days before administration	The patient received 1st to 4th courses of FEC100 therapy in succession (fluorouracil, epirubicin hydrochloride, cyclophosphamide hydrate) as preoperative chemotherapy.
				7 days before administration	The 1st course of docetaxel + trastuzumab was administered.
				Day 1 of administration	Administration of pegfilgrastim started on an outpatient basis. White blood cell count (WBC) was 1200/mm^3, CRP 0.99 mg/dL
				1 day after administration	The patient vomited twice and suffered pyrexia (37°C range)
				2 days after administration	Decreased appetite was noted and administration of levofloxacin hydrate was initiated.
				4 days after administration	The patient re-visited the outpatient unit. Vomiting and pyrexia (37°C range) occurred, WBC increased (60 400/mm^3). CRP was 5.99 mg/dL, LDH 1 534 IU/L. Febrile neutropenia was suspected. The patient was admitted to the hospital. Administration of loxoprofen sodium hydrate (60 mg×3/day) and prednisolone (10 mg×2/day) was initiated.
				5 days after administration	The patient recovered from decreased appetite.
				6 days after administration	Administration of prednisolone (10 mg×2/day) completed. Body temperature was 37.0°C, WBC 57 400/mm3, CRP 2.03 mg/dL.

				8 days after administration	Pyrexia (38°C range) was noted and aortitis developed. WBC was 33 700/mm3.
				9 days after administration	Symptoms improved with prednisolone (10 mg×2/day) and the patient was discharged.
				10 days after administration	The patient visited the emergency outpatient unit with pyrexia (39.0°C) and was admitted to the hospital. CT identified right pleural effusion. WBC was 21 600/mm3, CRP 30.08 mg/dL. Levofloxacin hydrate was administered but no improvement of the symptoms was observed. 2 sets of blood culture both tested negative.
				14 days after administration	Two units of packed red blood cell preparation were transfused for Hb 6.5g/dL
				15 days after administration	Chest, abdominal, and pelvic contrast CT detected bilateral pleural effusion and wall hypertrophy in the aortic arch, brachiocephalic artery, right subclavian artery, bilateral common carotid artery, and left subclavian artery. Body temperature was 36.9°C, WBC 12 400/mm3, CRP 25.82mg/dL.
				18 days after administration	Pyrexia (38.5°C) developed. WBC was 6 600/mm3, CRP 20.67 mg/dL Increased WBC was resolved. Two units of packed red blood cell preparation were transfused for Hb 6.9g/dL.
				19 days after administration	Administration of prednisolone (25 mg×1/day) was initiated.
				20 days after administration	Pyrexia resolved.
				21 days after administration	Cough, strange feeling of chest, and other symptoms related to aortitis were resolved and aortitis remitted.
				22 days after administration	Body temperature was 36.5°C, WBC 6 600/mm^3, CRP 5.77mg/dL.
				23 days after administration	The patients was discharged.
				29 days after administration	Dose of prednisolone was decreased (20 mg×1/day). Body temperature was 35.2°C, WBC 12 600/mm3, CRP 1.14 mg/dL.
				35 days after administration	The patient developed no pyrexia.
				42 days after administration	The 2nd course of docetaxel + trastuzumab was administered. Both drugs were decreased to 80% of the 1st course. Pegfilgrastim was not administered.
				49 days after administration	No recurrence of aortitis was observed.
				57 days after administration	Administration of prednisolone (20 mg×1/day) continued. CRP was 1.98 mg/dL

Laboratory Examination

	Day 1 of administration	4 days after administration	6 days after administration	8 days after administration	10 days after administration	12 days after administration	15 days after administration	18 days after administration	22 days after administration	29 days after administration
WBC (/mm3)	1 200	60 400	57 400	33 700	21 600	13 300	12 400	6 600	6 600	12 600
Neutrophil count (/mm3)	482	39 260	43 050	–	19 440	11 465	11 234	5 788	5 161	11 756
CRP (mg/dL)	0.99	5.99	2.03	–	30.08	26.53	25.82	20.67	5.77	1.14
LDH (IU/L)	241	1 534	680	–	343	240	153	151	163	200
Body temperature (°C)	–	37.0	37.0	38°C range	39.0	38.9	36.9	38.5	36.5	35.2
BP (sBP/dBP) (mmHg)	–	116/65	124/75	–	128/58	102/45	96/49	143/67	132/72	177/84
Heart rate (beats/min.)	–	86	70	–	84	76	66	74	62	83

Suspected concomitant medications:－

Concomitant medications: Fluorouracil, epirubicin hydrochloride, cyclophosphamide hydrate, docetaxel, trastuzumab, lansoprazole

3

Revision of Precautions (No. 295)

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated June 5, 2018, this section will present the details of revisions and branded names involved in these revisions.

1 Antiarrhythmic agents

Amiodarone hydrochloride

Branded name	[1] Ancaron tab. 100 (Sanofi K.K.), and the others [2] Ancaron inj. 150 (Sanofi K.K.), and the others
Adverse reactions (clinically significant adverse reactions)	**Agranulocytosis, leukopenia:** Agranulocytosis and/or leukopenia may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as discontinuation of administration, should be taken.

2 Blood and body fluid agents-Miscellaneous

[1] Pegfilgrastim (genetical recombination)
[2] Filgrastim (genetical recombination, including follow-on biologics)
[3] Lenograstim (genetical recombination)

Branded name	[1] G-Lasta Subcutaneous Injection 3.6 mg (Kyowa Hakko Kirin Co., Ltd.) [2] Gran Injection 75, 150, Gran Injection M300, Gran Syringe 75, 150, Gran Syringe M300 (Kyowa Hakko Kirin Co., Ltd.) and the other follow-on biologics [3] Neutrogin Injection 50 μg, 100 μg, 250 μg (Chugai Pharmaceutical Co., Ltd.)
Adverse reactions (clinically significant adverse reactions)	**Large vessel vasculitis (Inflammation in the aorta, common carotid artery, subclavian artery, or other large vessels):** 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.

3 Antineoplastics-Miscellaneous

Everolimus

Branded name	[1] Afinitor tablets 2.5 mg, 5 mg (Novartis Pharma K.K.) [2] Afinitor dispersible tablets 2 mg, 3 mg (Novartis Pharma K.K.)
Adverse reactions (clinically significant adverse reactions)	**Impaired wound healing:** Impaired wound healing may occur or lead to wound infection, incisional hernia, wound dehiscence, or other complications. If any abnormalities are observed, appropriate measures, such as discontinuation of administration, should be taken.

4 **Human blood preparations**

Eftrenonacog alfa (genetical recombination)

Branded name	Alprolix Intravenous 250, 500, 1000, 2000, 3000, 4000 (Vioverative Inc.)
Adverse reactions (clinically significant adverse reactions)	**Shock, anaphylaxis:** Shock or anaphylaxis may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

5 **Antiprotozoans, Antibiotics-Miscellaneous**

[1] Metronidazole (oral and injectable dosage forms)
[2] Lansoprazole/amoxicillin hydrate/metronidazole
[3] Rabeprazole sodium/amoxicillin hydrate/metronidazole
[4] Vonoprazan fumarate/amoxicillin hydrate/metronidazole

Branded name	[1] Flagyl Oral Tablets 250 mg (Shionogi & Co., Ltd.), Anaemetro Intravenous infusion 500 mg (Pfizer Japan Inc.) [2] Lampion Pack (Takeda Pharmaceutical Company Limited) [3] Rabefine Pack (Eisai Co., Ltd.) [4] Vonopion Pack (Takeda Pharmaceutical Company Limited)
Careful Administration	Patients with Cockayne's syndrome
Important precautions	Hepatic impairment may occur. Patients should be carefully monitored through methods such as periodic examinations.
Adverse reactions (clinically significant adverse reactions)	**Hepatic impairment:** Hepatic impairment may occur. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken. Severe hepatotoxicity or acute hepatic failure resulting in mortality has been reported in patients with Cockayne's syndrome.

4

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for newly-approved drug products refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. The MAH responsible for a new drug in the EPPV period is required to collect ADR data from all medical institutions where the drug is used and to take safety measures as appropriate. The aim of EPPV is to promote the rational and appropriate use of drugs in medical treatments and to facilitate prompt action for the prevention of serious ADRs. EPPV is specified as a condition of product approval.

(As of May 31, 2018)
◎: Products for which EPPV was initiated after May 1, 2018

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Migalastat hydrochloride Galafold Capsules 123 mg	Amicus Therapeutics, Inc.	May 30, 2018
◎	Letermovir Prevymis Tablets 240 mg, Prevymis Intravenous Infusion 240 mg	MSD K.K.	May 28, 2018
◎	Mepolizumab (genetical recombination) [*1] Nucala for S.C. Injection 100 mg	GlaxoSmithKline K.K.	May 25, 2018
◎	Ipilimumab (genetical recombination) Yervoy Injection 50 mg	Bristol-Myers Squibb K.K.	May 25, 2018
◎	Nivolumab (genetical recombination) Opdivo I.V. Infusion 20 mg, 100 mg	Ono Pharmaceutical Co., Ltd.	May 25, 2018
◎	Botulinum toxin type A [*2] Botox for Injection 50 Units, 100 Units	GlaxoSmithKline K.K.	May 25, 2018
◎	Tofacitinib citrate [*3] Xeljanz Tablets 5 mg	Pfizer Japan Inc.	May 25, 2018
◎	Emicizumab (genetical recombination) Hemlibra Subcutaneous Injection 30 mg, 60mg, 90 mg, 105 mg, 150 mg	Chugai Pharmaceutical Co., Ltd.	May 22, 2018
◎	Guselkumab (genetical recombination) Tremfya Subcutaneous Injection 100 mg Syringe	Janssen Pharmaceutical K.K.	May 22, 2018
◎	Evocalcet Orkedia Tablets 1 mg, 2 mg	Kyowa Hakko Kirin Co., Ltd.	May 22, 2018
◎	Hydromorphone hydrochloride Naruvein Injection 2 mg, 20 mg	Daiichi Sankyo Propharma Co., Ltd.	May 16, 2018
◎	Bedaquiline fumarate Sirturo Tablets 100 mg	Janssen Pharmaceutical K.K.	May 8, 2018
	Ezetimibe/atorvastatin calcium hydrate Atozet Combination Tablets LD, HD	MSD K.K.	April 23, 2018
	Dupilumab (genetical recombination) Dupixent S.C. Injection 300 mg Syringe	Sanofi K.K.	April 23, 2018

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Elobixibat hydrate Goofice Tablets 5 mg	EA Pharma Co., Ltd.	April 19, 2018
Olaparib Lynparza Tablets 100 mg, 150 mg	AstraZeneca K.K.	April 18, 2018
Inotuzumab ozogamicin (genetical recombination) Besponsa Injection 1mg	Pfizer Japan Inc.	April 18, 2018
Benralizumab (genetical recombination) Fasenra Subcutaneous Injection 30 mg Syringe	AstraZeneca K.K.	April 18, 2018
Brexpiprazole Rexulti Tablets 1 mg, 2 mg	Otsuka Pharmaceutical Co., Ltd.	April 18, 2018
Atezolizumab (genetical recombination) Tecentriq I.V. Infusion 1200 mg	Chugai Pharmaceutical Co., Ltd.	April 18, 2018
Romidepsin Istodax Injection 10 mg	Celgene Corporation	April 18, 2018
Baloxavir marboxil Xofluza Tablets 10 mg, 20mg	Shionogi & Co., Ltd.	March 14, 2018
Abatacept (genetical recombination)*4 Orencia for I.V. Infusion 250 mg	Bristol-Myers Squibb K.K.	February 23, 2018
Sarilumab (genetical recombination) Kevzara 150 mg, 200 mg Syringe for SC Injection	Sanofi K.K.	February 5, 2018
Sildenafil citrate Revatio Dry Syrup for Suspension 900 mg,	Pfizer Japan Inc.	January 29, 2018
Esomeprazole magnesium hydrate Nexium Capsules 10 mg, 20 mg, Nexium Granules for Suspension 10 mg, 20 mg	AstraZeneca K.K.	January 19, 2018
Eculizumab (genetical recombination)*5 Soliris for Intravenous Infusion 300 mg	Alexion Pharma G.K.	December 25, 2017
Aminolevulinic acid hydrochloride*6 Alaglio Divided Granules 1.5 g	SBI Pharmaceuticals Co., Ltd.	December 19, 2017
Palbociclib Ibrance Capsules 25 mg, 125 mg	Pfizer Japan Inc.	December 15, 2017
Belimumab (genetical recombination) Benlysta for I.V. Infusion 120 mg, 400 mg Benlysta for S.C. Injection 200 mg Autoinjector, 200 mg Syringe	GlaxoSmithKline K.K.	December 13, 2017
Bezlotoxumab (genetical recombination) Zinplava for Intravenous Drip Infusion 625 mg	MSD K.K.	December 8, 2017
Budesonide Rectabul 2 mg Rectal Foam 14 Doses	EA Pharma Co., Ltd.	December 7, 2017
Lonoctocog alfa (genetical recombination) Afstyla I.V. Injection 250, 500, 1000, 1500, 2000, 2500, 3000	CSL Behring K.K.	December 1, 2017

*1 Eosinophilic granulomatosis with polyangiitis that does not adequately respond to existing treatments

*2 Spasmodic dysphonia

*3 Remission induction or remission maintenance therapy for moderate to severe active ulcerative colitis

*4 Polyarticular juvenile idiopathic arthritis that does not adequately respond to existing treatments

*5 Generalized myasthenia gravis (for use only in patients whose symptoms are difficult to control with high-

dose intravenous immunoglobulin therapy or hemocatharsis)

*6 Visualization of tumor tissues of the non-muscle invasive bladder cancer in transurethral resection of bladder tumor