Pharmaceuticals and Medical Devices Safety Information

No. 389 January 2022

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* publication is issued reflective of safety information collected by the Ministry of Health, Labour and Welfare (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) Medical Product Information web page (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, only available in Japanese language).

Available information is listed here

Access to the latest safety information is available via the PMDA Medi-navi.

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This English version of PMDSI is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of this English version.

Pharmaceuticals and Medical Devices Safety Information

No. 389 January 2022

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

[Outline of Information]

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

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

If medical and pharmaceutical providers 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 medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADE	Adverse drug event
ADR	Adverse drug reaction
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal Year
GAD	General Affairs Division
GVHD	Graft versus host disease
HPB	Health Policy Bureau
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
MSPO	Office of Medical Safety Promotion
PIM	Potentially inappropriate medication
PMDA	Pharmaceuticals and Medical Devices Agency
PSD	Pharmaceutical Safety Division
PSEHB	Pharmaceutical Safety and Environmental Health Bureau

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How to Start and Proceed with Improving Polypharmacy among the Elderly in Hospitals

1. Introduction

In association with the growth of the aging population, safety problems readily occur from concomitant administration of multiple drugs due to physiological change by age and treatment of multiple comorbidities. MHLW established the Study Group on the Appropriate Medication for Elderly Patients (hereinafter referred to as the “Study Group”) in April 2017 and has been working on investigations and consideration of the matters necessary to secure safety of drug therapy in the elderly.

The Study Group has worked on compiling the Guidances on Appropriate Medication for Elderly Patients and in fiscal year (FY) 2020, the Study Group also compiled How to Start and Proceed with Improving Polypharmacy* among the Elderly in Hospitals, as the operational procedures and a collection of example forms (hereinafter referred to as "Operational Procedures, etc.") for an aid in starting efforts to devise polypharmacy measures and in systematically establishing and running operational systems.

This section will introduce the Study Group’s past efforts and the Operational Procedures, etc. as an aid for medical institutions in their efforts to implement polypharmacy measures.

*Polypharmacy: A condition that denotes not simply using numerous medications concurrently, but rather the various concerns that this practice can lead to, such as increased risk of adverse drug events (ADEs), medication errors, and decreased medication adherence, among others

2. Past efforts related to polypharmacy measures

The Study Group first compiled the Guidance on Appropriate Medication for Elderly Patients (general) for the purpose of optimization of drug therapy in the elderly (avoidance of ADEs, improvement of drug adherence, avoidance of insufficient medical treatment), and as the basic considerations for better drug therapy in view of the characteristics of the elderly. In addition, the particulars (by recuperation environment) of the guidance were compiled to clarify the points to be considered for each treatment environment of patients, taking into account the fact that such considerations required for those concerned change as patients' conditions, lives, and environments change. The MHLW issued notifications of these guidances in May 2018 and June 2019, respectively, for the use of medical institutions. In FY2019, in order to further promote appropriate drug therapy for the elderly, a questionnaire survey was conducted among hospitals with more than 100 beds to ascertain the actual status of the use of the two guidances and the proper use of drugs by the elderly. In addition, local polypharmacy measures were investigated for good practice examples, and they were compiled in a collection of examples.

The survey revealed that 50% of the respondents had a precise understanding of polypharmacy including the definition, and approximately 60% in total had a good understanding or some understanding of the guidances compiled by the Study Group. However, only 6% of the respondents answered that "there are procedures and other rules/regulations aimed at eliminating polypharmacy that cite the contents of the guidances," and 5% answered that "special conferences are being held to deal with polypharmacy in individual patients.”

3. How to Start and Proceed with Improving Polypharmacy for the Elderly in Hospitals

As a result of the survey, it was found that while there is a certain level of understanding of polypharmacy and the two guidances, it is difficult to believe that there is sufficient progress in the efforts for polypharmacy measures, and that it is difficult to directly implement advanced measures such as those implemented in the good practice facilities. The need for a more practical tool that can be used by medical institutions was suggested. Based on these results, the Study Group discussed the issues and compiled the How to Start and Proceed with Improving Polypharmacy among the Elderly in Hospitals as the operational procedures, etc., to be used for an aid in starting efforts to devise polypharmacy measures and in systematically establishing and running operational systems.

One of the purposes of the procedures, etc. is to be used as a start-up tool for hospitals launching their polypharmacy measures in order to solve the problems they will face in the early stages of their efforts. The responses for this purpose are summarized in Chapter 1, How to Start Polypharmacy Measures. Another purpose is for hospitals that have already taken polypharmacy measures to some extent to use them as reference materials in preparing their own operational procedures and making their operations more efficient. This purpose is addressed in Chapter 2, How to Proceed with Polypharmacy Measures. Since cooperation with medical and nursing care professionals who are responsible for the comprehensive community care system is essential when patients return to the community, cooperation with related facilities in the community is also described.

While intended for physicians, dentists, and pharmacists as the main users, the procedures, etc. also assume use by healthcare professionals who are involved in the polypharmacy measures in a broader sense. In addition, although the procedures, etc. assume hospitals as the scene of use, active use in clinics and pharmacies of applicable contents is also hoped for.

This section introduces the outline of the efforts below.

Chapter 1: How to Start Polypharmacy Measures

✧ Before starting polypharmacy measures

Rather than focusing only on a uniform number of drugs or of types of drugs, it is necessary to understand that prescriptions must be optimized in terms of ensuring safety, etc., in starting polypharmacy measures. Specifically, the following must be acknowledged:

□Understand the current situation in the hospital

□Cultivate deeper understanding in the hospital

□Seek understanding from related facilities outside the hospital

✧ Beginning with small issues

□ Decide who will be in charge.

□ Start small.

□ Select patients for polypharmacy measures within the capacity for care.

□ Utilize already existing arrangements and tools (Table 1).

□Table 1　How to adopt polypharmacy measures for existing tools

Job category	Tool	Utilization strategy
Physicians and dentists	Medical information form	・Add a column for details and reasons for prescription revision. ・ Add a column for pharmacists to summarize medications.
Pharmacists in the pharmacy department, etc.	Record format for medications brought in at admission	Add a check box for suspected polypharmacy and a column to state the reason for the suspicion.
	Medication management summary	Note the details of the prescription revision with reasons.
	Medication record book	Note the details of the prescription revision with reasons.
	Medication information form	Details of prescription revision with the reasons should be noted in the column for pharmacists to summarize medications and others.
Nurses	Nursing summary	Add a column for details and reasons for prescription revision.
Administrative staff, etc.	Electronic medical record	Customize the electronic medical record to incorporate the perspective of polypharmacy measures. (e.g.) A warning message should be arranged to come off in response to drugs falling under the category of PIMs*.
Pharmacy pharmacist	Medication information form	Add a column for patients' intentions, proposed revision of prescription and reasons for it, for them to fill in.

*PIMs: Potentially inappropriate medications that require extremely careful administration

✧ Challenges and responses in starting polypharmacy measures

Responses to challenges such as "too understaffed to make time to identify polypharmacy patients or to consider polypharmacy measures," "insufficient cooperation with other job categories," "Medication record book underutilized," "Difficulty determining whether a patient is under polypharmacy or not," "Difficulty for a physician to adjust medications prescribed in other departments," "Difficulty grasping comprehensive disease conditions," "A system yet to be arranged to feedback the revised prescription details to primary physicians," "Difficulty obtaining patients' understanding."

Chapter 2: How to start polypharmacy measures

✧ Setting up a system for polypharmacy measures

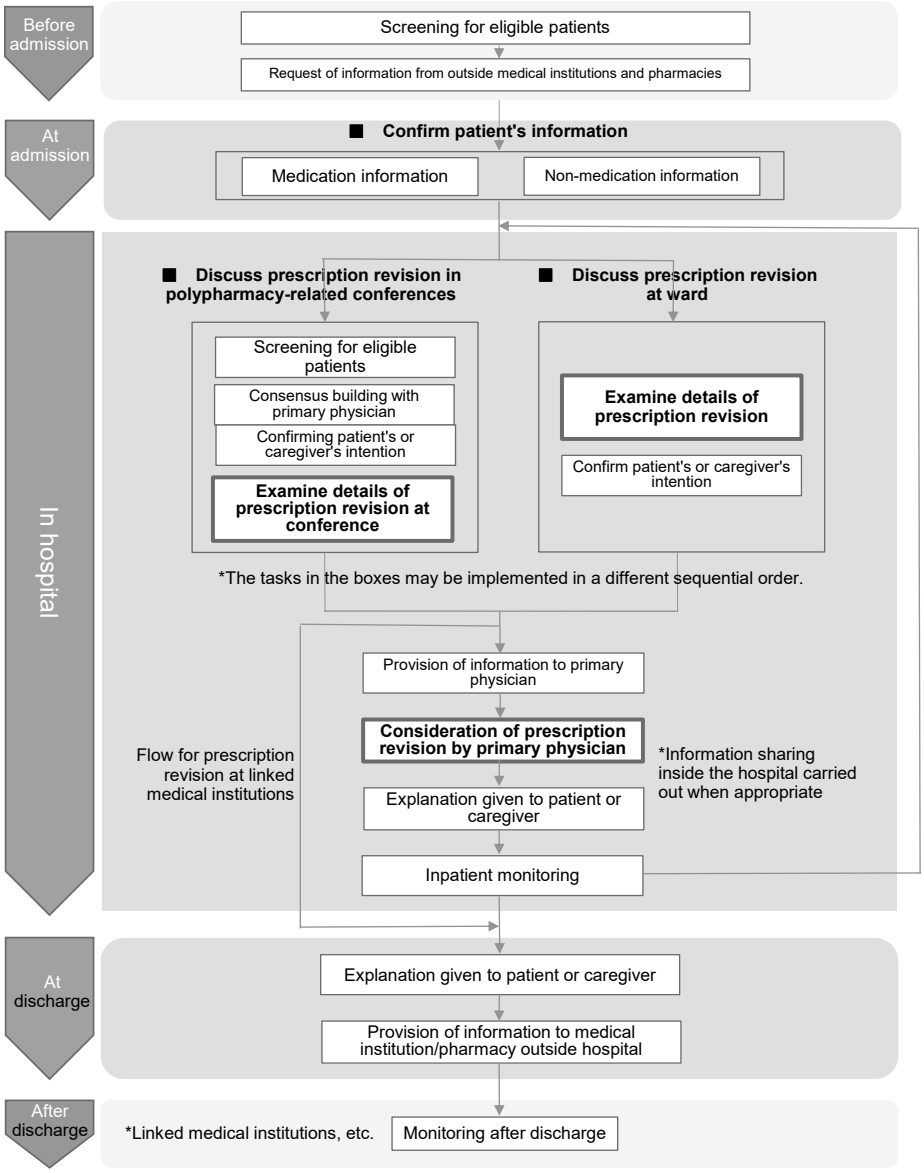
- Review the concept of polypharmacy.
- Identify the purposes of polypharmacy measures.
- Assemble related materials.

- Develop operating rules.
- Develop a staffing structure.
- Develop a cooperation structure with medical and nursing care professionals, etc., who are responsible for the comprehensive community care system.
- Monitor results of polypharmacy measures.
- Promote digitization of polypharmacy measures.
- Consider the costs.

✧ Implementation of polypharmacy measures

Specific procedures and considerations in implementing polypharmacy measures are presented as responses to inpatients along the course from prior to, during, and after admission (Figure 1), as well as responses for outpatients and educational activities for staff.

Figure 1　Flow of responses for inpatients



Note: “Polypharmacy-related conference” includes existing medical team conferences if polypharmacy is discussed.

✧ Collection of example forms

Examples of forms to be used in polypharmacy measures (preparing rules, identifying patients suspected of polypharmacy, providing information on the results of prescription revision, and monitoring of patients' conditions after prescription revision) are contained.

4. Closing remark

The How to Start and Proceed with Improving Polypharmacy among the Elderly in Hospitals and the Guidances on Appropriate Medication for Elderly Patients introduced here are available on the MHLW's website (see reference below) for reference and use in polypharmacy measures. The Study Group's past efforts and current discussions for polypharmacy are also listed in the reference.

Continued consideration of the concerned parties for the safety measures for drugs would be appreciated.

[References]

- Guidance on Appropriate Medication for Elderly Patients (general)
  (HPB/GAD/MSPO 0529 No.1, PSEHB/PSD 0529 No.1 dated May 29, 2018)
  https://www.mhlw.go.jp/stf/shingi2/0000208848.html (Japanese)
  https://www.pmda.go.jp/files/000232249.pdf (English)
- Guidance of Appropriate Medication for Elderly Patients [particular (by recuperation environment)]
  (HPB/GAD/MSPO 0614 No.1, PSEHB/PSD 0614 No.1 dated June 14, 2019)
  https://www.mhlw.go.jp/stf/newpage_05217.html (only in Japanese)
- FY2019 Survey on the Polypharmacy Measures in Clinical Practice
  (Material 1, the 11th Study Group on the Appropriate Medication for Elderly Patients on April 10, 2020)
  https://www.mhlw.go.jp/content/11125000/000622768.pdf (only in Japanese)
- How to Start and Proceed with Improving Polypharmacy among the Elderly in Hospitals
  (HPB/GAD/MSPO 0331 No.1, PSEHB/PSD 0331 No.1 dated March 31, 2021)
  https://www.mhlw.go.jp/content/11120000/000763323.pdf (only in Japanese)
- Study Group on the Appropriate Medication for Elderly Patients
  http://www.mhlw.go.jp/stf/shingi/other-iyaku.html?tid=431862 (only in Japanese)

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Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated December 17, 2021, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 Fingolimod hydrochloride

Brand name (name of company)	a. Imusera Capsules 0.5 mg (Mitsubishi Tanabe Pharma Corporation) b. Gilenya Capsules 0.5 mg (Novartis Pharma K.K.)
Therapeutic category	Agents affecting metabolism, n.e.c. (not elsewhere classified)
Indications	Prevention of relapse and delay of progression of physical disability in multiple sclerosis

PRECAUTIONS (revised language is underlined)

[Under new instructions]

8. IMPORTANT PRECAUTIONS (newly added)	Thrombocytopenia may occur. Blood tests (such as blood cell count) should be performed prior to, and periodically during, administration of this drug. Cases of severe exacerbation of disease compared with before administration have been reported following discontinuation of this drug, generally observed up to 24 weeks after discontinuation. When administration is discontinued, caution should be exercised for severe aggravation of disease.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Thrombocytopenia
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) reported during the previous approximately 3-year period (April 2018 to March 2020) Cases involving thrombocytopenia : 0 Cases involving severe exacerbation of disease after discontinuation: 18 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: [1] Approximately 2 385 [2] Approximately 1 200 Japanese market launch: [1] [2] November 2011

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
1	Female 40s	Multiple sclerosis (none)	0.5 mg 615 days	**Multiple sclerosis relapse** Before administration: The patient had difficulty using her right hand. Lower extremities deep sensation decreased. Symptoms: Sensory system symptoms present MRI: Multiple lesions found in the periventricular white matter, cervical and thoracic spinal cord, Cerebral lesions: Yes, Cerebellar lesions: No, Brain stem lesions: No, Optic lesions: No, Spinal lesions: Yes Day 1 of administration: Administration of fingolimod hydrochloride was initiated. Day 615 of administration (Day of discontinuation): Fingolimod hydrochloride was discontinued due to concerns about progressive multifocal leukoencephalopathy (PML), etc. 28 days after discontinuation: Brain MRI findings were stable. 36 days after discontinuation: Administration of dimethyl fumarate was initiated. 91 days after discontinuation: MRI: Many multifocal mass-like spinal cord lesions and recurrent lesions were confirmed. Cerebral lesions: Yes, Cerebellar lesions: No, Brain stem lesions: No, Optic lesions: No, Spinal lesions: Yes Symptoms: Paresis/paralysis, numbness Steroid pulse therapy was performed. 119 days after discontinuation: Brain MRI observed an enhanced new lesion. 173 days after discontinuation: MRI confirmed many enhanced new lesions and recurrent lesions. Steroid pulse therapy was performed. 301 days after discontinuation: MRI confirmed many new lesions and recurrent lesions. Steroid pulse therapy was performed. 419 days after discontinuation: MRI confirmed many new lesions and recurrent lesions. Steroid pulse therapy was performed. 465-525 days after discontinuation: 7 cycles of immunoadsorption therapy were performed. 525 days after discontinuation: Final diagnosis: Multiple sclerosis relapse Multiple sclerosis relapse was not resolved.

Laboratory test value

	Before administration	Day of discontinuation	28 days after discontinuation	After onset of adverse reactions
EDSS*	1.5	—	—	1.5
Lymphocyte count (/μL)	—	479	1191	—

*Expanded Disability Status Scale

Suspected concomitant drugs: Dimethyl fumarate
Concomitant drugs: Urapidil, pregabalin, famotidine, flavin adenine dinucleotide sodium, polycarbophil calcium, clostridium butyricum preparation

3
Revision of Precautions (No.329)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated December 3, December 8, and December 17, 2021.

1 Vaccines
Coronavirus modified uridine RNA vaccine (SARS-CoV-2)

Brand name
[Under New instructions]
Comirnaty intramuscular injection (Pfizer Japan Inc.)

8. IMPORTANT PRECAUTIONS

Shock, anaphylaxis may occur. Vaccine recipients should be carefully questioned regarding their history of hypersensitivity prior to, and preferably be monitored for their conditions for a certain amount of time following, inoculation with this vaccine. In addition, individuals who have developed shock, anaphylaxis following inoculation with this vaccine should not be inoculated with this vaccine thereafter.
Myocarditis, pericarditis may occur. Vaccine recipients or their caregivers should be instructed in advance to seek medical attention immediately if they experience or notice any symptoms that could suggest myocarditis or pericarditis (such as chest pain, palpitation, oedema, dyspnoea, and tachypnoea).

11. ADVERSE REACTIONS

Shock, anaphylaxis

11.1 Clinically Significant Adverse Reactions (newly added)

Myocarditis, pericarditis

11.2 Other Adverse Reactions (newly added)

Site	Adverse reactions
Immune system	Hypersensitivity (rash, pruritus, erythema, urticarial, angioedema, facial swelling, etc.)

15. OTHER PRECAUTIONS

15.1 Information Based on Clinical Use

Cases of myocarditis and pericarditis have been reported overseas following inoculation with coronavirus modified uridine RNA vaccine (SARS-CoV-2). Reported cases for the initial immunization have occurred predominantly in male adolescents and young adults and onset was typically within several days after the second vaccination. It has also been reported that in most cases, patients had improvement of symptoms by resting in a supine position in hospital.

(newly added)

It is suggested that the frequency of myocarditis and pericarditis was higher in the male adolescents and young adults following the second inoculation with this vaccine for the initial immunization by comparing the reporting rates of myocarditis and pericarditis in the domestic suspected adverse reaction reports after the start of vaccination and the estimated background incidence rates of myocarditis and pericarditis in the general population utilizing a domestic medical information database.
Although the causal relationship is unknown, cases of localized swelling (particularly in the face) that developed around the areas of filler placements following inoculation with Coronavirus modified uridine RNA vaccine (SARS-CoV-2) have been reported overseas in vaccine recipients with a history of injection of dermatological fillers.

2 Vaccines
Coronavirus modified uridine RNA vaccine (SARS-CoV-2)

Brand name	Spikevax Intramuscular Injection (previously COVID-19 Vaccine Moderna Intramuscular Injection) (Takeda Pharmaceutical Company Limited.)
[Under New instructions]	
8. IMPORTANT PRECAUTIONS	Myocarditis, pericarditis may occur. Vaccine recipients or their caregivers should be instructed in advance to seek medical attention immediately if they experience or notice any symptoms that could suggest myocarditis or pericarditis (such as chest pain, palpitation, oedema, dyspnoea, and tachypnoea).
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Myocarditis, pericarditis
15. OTHER PRECAUTIONS **15.1 Information Based on Clinical Use**	Cases of myocarditis and pericarditis have been reported overseas following inoculation with coronavirus modified uridine RNA vaccine (SARS-CoV-2). Reported cases for the initial immunization have occurred predominantly in male adolescents and young adults and onset was typically within several days after the second vaccination. It has also been reported that in most cases, patients had improvement of symptoms by resting in a supine position in hospital. It is suggested that the frequency of myocarditis and pericarditis was higher in the male adolescents and young adults following the second inoculation with this vaccine by comparing the reporting rates of myocarditis and pericarditis in the domestic suspected adverse reaction reports after the start of vaccination and the estimated background incidence rates of myocarditis and pericarditis in the general population utilizing a domestic medical information database.
(newly added)	Although the causal relationship is unknown, cases of localized swelling (particularly in the face) that developed around the areas of filler placements following inoculation with Coronavirus modified uridine RNA vaccine (SARS-CoV-2) have been reported overseas in vaccine recipients with a history of injection of dermatological fillers.

3 Other agents for epidermis
Tacrolimus hydrate (ointment 0.1%)

Brand name	Protopic Ointment 0.1% (Maruho Co., Ltd.)
[Under Old instructions]	
Warnings	(deleted)
Important Precautions **(newly added)**	The immunosuppressive effects of this drug present a potential risk of carcinogenicity. In the long-term post-marketing survey conducted in Japan with the 0.03% preparation, no cases of malignant lymphoma, skin cancer or other malignant tumor have been reported. No increase in the risk of carcinogenicity associated with this drug was observed either in an overseas long-term epidemiological study. On the other hand, cases of malignant lymphoma or skin cancer have been reported in patients treated with this drug, although the causal relationship is not clear. When this drug is used, such information should be made known to patients and their understanding should be ensured prior to administration. (deleted)

Other Precautions (newly added)	In order to assess the long-term carcinogenic risk of this drug, an epidemiological study (a prospective cohort study for 10 years) was conducted overseas in pediatric patients with atopic dermatitis. During 44 629 person-years of observation, malignant tumor was reported in 6 cases and the standardized incidence ratio relative to the expected number of 5.95 cases in the sex- and age-matched population was 1.01 (95% CI: 0.37 to 2.20).
[Under New instructions]	
1. WARNINGS	(deleted)
8. IMPORTANT PRECAUTIONS	The immunosuppressive effects of this drug present a potential risk of carcinogenicity. In the long-term post-marketing survey conducted in Japan with the 0.03% preparation, no cases of malignant lymphoma, skin cancer or other malignant tumor have been reported. No increase in the risk of carcinogenicity associated with this drug was observed either in an overseas long-term epidemiological study. On the other hand, cases of lymphoma or skin cancer have been reported in patients treated with this drug, although the causal relationship is not clear. When this drug is used, such information should be made known to patients and their understanding should be ensured prior to administration. (deleted)
15. OTHER PRECAUTIONS (newly added)	In order to assess the long-term carcinogenic risk of this drug, an epidemiological study (a prospective cohort study for 10 years) was conducted overseas in pediatric patients with atopic dermatitis. During 44 629 person-years of observation, malignant tumor was reported in 6 cases and the standardized incidence ratio relative to the expected number of 5.95 cases in the sex- and age-matched population was 1.01 (95% CI: 0.37 to 2.20).

4 Other agents for epidermis

Tacrolimus hydrate (ointment 0.03%)

Brand name	Protopic Ointment 0.03% for Pediatric (Maruho Co., Ltd.)
[Under New instructions]	
1. WARNINGS	(deleted)
8. IMPORTANT PRECAUTIONS (newly added)	The immunosuppressive effects of this drug present a potential risk of carcinogenicity. In the long-term post-marketing survey conducted in Japan, no cases of malignant lymphoma, skin cancer, or other malignant tumor have been reported. No increase in the risk of carcinogenicity associated with this drug was observed either in an overseas long-term epidemiological study. On the other hand, cases of malignant lymphoma or skin cancer have been reported in patients treated with this drug, although the causal relationship is not clear. When this drug is used, such information should be made known to patients or caregivers and their understanding should be ensured prior to administration. (deleted)
15. OTHER PRECAUTIONS (newly added)	In order to assess the long-term carcinogenic risk of this drug, an epidemiological study (a prospective cohort study for 10 years) was conducted overseas in pediatric patients with atopic dermatitis. During 44 629 person-years of observation, malignant tumor was reported in 6 cases and the standardized incidence ratio relative to the expected number of 5.95 cases in the sex- and age-matched population was 1.01 (95% CI: 0.37 to 2.20).

5 Psychotropic agents

Blonanserin (oral dosage form)

Brand name

Lonasen Tablets 2 mg, 4 mg, 8 mg, Lonasen Powder 2%, Lonasen Tapes 20 mg, 30 mg, 40 mg (Sumitomo Dainippon Pharma Co., Ltd.)

[Under Old instructions]

Contraindications

Patients receiving azole antifungal agents (itraconazole, voriconazole, miconazole (oral dosage form, oral preparation, injectable dosage forms), fluconazole, fosfluconazole, posaconazole), HIV protease inhibitors (ritonavir, lopinavir/ritonavir combination agents, nelfinavir, darunavir, atazanavir, fosamprenavir), or preparations containing cobicistat

Drug Interactions
Contraindications for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Drugs that strongly inhibit CYP3A4 [Azole antifungal agents (itraconazole, voriconazole, miconazole (oral dosage form, oral preparation, injectable dosage form), fluconazole, fosfluconazole, posaconazole), HIV protease inhibitors (ritonavir, lopinavir/ritonavir combination agents, nelfinavir, darunavir, atazanavir, fosamprenavir), preparations containing cobicistat]	The blood concentration of this drug may increase, and the effects may be enhanced.	Oral clearance may decrease since these drugs inhibit CYP3A4, the major metabolic enzymes of this drug. It has been reported overseas that the AUC and C_{max} of this drug increased 17-fold and 13-fold, respectively, when co-administered with ketoconazole (oral dosage form; not marketed in Japan).

[Under New instructions]

2. CONTRAINDICATIONS

Patients receiving azole antifungal agents (itraconazole, voriconazole, miconazole (oral dosage form, oral preparation, injectable dosage forms), fluconazole, fosfluconazole, posaconazole), HIV protease inhibitors (ritonavir, lopinavir/ritonavir combination agents, nelfinavir, darunavir, atazanavir, fosamprenavir), or preparations containing cobicistat

10. INTERACTIONS
10.1 Contraindications for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Drugs that strongly inhibit CYP3A4 [Azole antifungal agents (itraconazole, voriconazole, miconazole (oral dosage form, oral preparation,	The blood concentration of this drug may increase, and the effects may	Oral clearance may decrease since these drugs inhibit CYP3A4, the major metabolic

injectable dosage forms), fluconazole, fosfluconazole ,posaconazole), HIV protease inhibitors (ritonavir, lopinavir/ritonavir combination agents, nelfinavir, darunavir, atazanavir, fosamprenavir), preparations containing cobicistat]	be enhanced.	enzymes of this drug. It has been reported overseas that the AUC and C_{max} of this drug increased 17-fold and 13-fold, respectively, when co-administered with ketoconazole (oral dosage form; not marketed in Japan).

6 Psychotropic agents

Blonanserin (patches)

Brand name Lonasen Tablets 2 mg, 4 mg, 8 mg, Lonasen Powder 2%, Lonasen Tapes 20 mg, 30 mg, 40 mg (Sumitomo Dainippon Pharma Co., Ltd.)

[Under New instructions]

2. CONTRAINDICATIONS Patients receiving azole antifungal agents (itraconazole, voriconazole, miconazole (oral dosage form, oral preparation, injections), fluconazole, fosfluconazole, posaconazole), HIV protease inhibitors (ritonavir, lopinavir/ritonavir combination agents, nelfinavir, darunavir, atazanavir, fosamprenavir), or preparations containing cobicistat

10. INTERACTIONS
10.1 Contraindications for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Drugs that strongly inhibit CYP3A4 [Azole antifungal agents (itraconazole, voriconazole, miconazole (oral dosage form, oral preparation, injections), fluconazole, fosfluconazole, posaconazole), HIV protease inhibitors (ritonavir, lopinavir/ritonavir combination agents, nelfinavir, darunavir, atazanavir, fosamprenavir), preparations containing cobicistat]	The blood concentration of this drug may increase, and the effects may be enhanced.	Clearance may decrease since these drugs inhibit CYP3A4, the major metabolic enzymes of this drug.

7 Other agents affecting central nervous system

Suvorexant

Brand name Belsomra Tablets 10 mg, 15 mg, 20 mg (MSD K.K.)

[Under Old instructions]

Contraindications Patients receiving drugs that strongly inhibit CYP3A (itraconazole, posaconazole, clarithromycin, ritonavir, nelfinavir,

voriconazole)

Drug Interactions Contraindications for Co-administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Drugs that strongly inhibit CYP3A (itraconazole, posaconazole clarithromycin, ritonavir, nelfinavir, voriconazole)	These drugs should not be co-administered since they may enhance the effects of this drug markedly.	These drugs strongly inhibit CYP3A, the metabolic enzymes of suvorexant and markedly increase the plasma concentration of suvorexant.

8 Agents affecting metabolism, n.e.c. (not elsewhere classified)

Fingolimod hydrochloride

Brand name

[1] Imusera Capsules 0.5 mg (Mitsubishi Tanabe Pharma Corporation)
[2] Gilenya Capsules 0.5 mg (Novartis Pharma K.K.)

[Under New instructions]

8. IMPORTANT PRECAUTIONS (newly added)

Thrombocytopenia may occur. Blood tests (such as blood cell count) should be performed prior to, and periodically during, administration of this drug.
Cases of severe exacerbation of disease compared with before administration have been reported following discontinuation of this drug, generally observed up to 24 weeks after discontinuation. When administration is discontinued, caution should be exercised for severe aggravation of disease.

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions (newly added)

Thrombocytopenia

9 Antibiotic preparations acting mainly on mold

Posaconazole

Brand name

Noxafil Tablets 100 mg, Noxafil for Intravenous Infusion 300 mg (MSD K.K.)

[Under New instructions]

2. CONTRAINDICATIONS

Patients receiving ergotamine tartrate/anhydrous caffeine/ isopropylantipyrine, dihydroergotamine, methylergometrine, ergometrine, simvastatin, atorvastatin, pimozide, quinidine, venetoclax [during its dose escalation phase for relapsed or refractory chronic lymphocytic leukemia (including small lymphocytic lymphoma)], suvorexant, lurasidone hydrochloride, or blonanserin

10. INTERACTIONS

Drugs	Signs, Symptoms,	Mechanism and Risk Factors

10.1 Contraindications for Co-administration (newly added)

	and Treatment	
Suvorexant	The effects of suvorexant may be enhanced markedly.	The plasma concentration of suvorexant is expected to rise due to inhibition of CYP3A4 by co-administration with posaconazole.
Lurasidone hydrochloride, blonanserin	The effects of these drugs may be enhanced.	The blood concentration of these drugs is expected to rise due to inhibition of CYP3A4 by co-administration with posaconazole.

10 Human blood preparations

[1] Concentrated human blood platelet (non-irradiated preparations)
[2] Synthetic blood (non-irradiated preparations)
[3] Washed human red blood cell (non-irradiated preparations)

Brand name

[1] Platelet Concentrate, Leukocytes Reduced, NISSEKI (PC-LR) (Japanese Red Cross Society), Platelet Concentrate HLA, Leukocytes Reduced, NISSEKI (PC-HLA-LR) (Japanese Red Cross Society)
[2] Blood for Exchange Transfusion, Leukocytes Reduced, NISSEKI (BET-LR) (Japanese Red Cross Society)
[3] Washed Red Cells, Leukocytes Reduced, NISSEKI (WRC-LR) (Japanese Red Cross Society)

[Under Old instructions]

Warnings

Cases of pyrexia and erythema that developed 1 to 2 weeks after transfusion of this drug, followed by death from graft versus host disease (GVHD) accompanied by diarrhoea, hepatic impairment, granulocytopenia, etc. have been rarely reported. Radiation at 15 to 50 Gy should be applied to this drug prior to transfusion.

Precautions Concerning Dosage and Administration (newly added)

Irradiation: Radiation at 15 to 50 Gy should be applied to this drug prior to transfusion.

Adverse Reactions and Infections
Clinically Significant Adverse Reactions and Infections

GVHD: Cases of pyrexia and erythema that developed 1 to 2 weeks after transfusion of this drug, followed by death from GVHD accompanied by diarrhoea, hepatic impairment, granulocytopenia, etc. have been reported.

11 Human blood preparations

[1] Human red blood cells (non-irradiated preparations)
[2] Whole human blood (non-irradiated preparations)

Brand name

[1] Red Blood Cells, Leukocytes Reduced, NISSEKI (RBC-LR) (Japanese Red Cross Society)
[2] Whole Blood, Leukocytes Reduced, NISSEKI (WB-LR) (Japanese Red Cross Society)

[Under Old instructions]

Warnings

Cases of pyrexia and erythema that developed 1 to 2 weeks after transfusion of this drug, followed by death from graft versus host disease (GVHD) accompanied by diarrhoea, hepatic impairment, granulocytopenia, etc. have been rarely reported. Radiation at 15 to 50 Gy should be applied to this drug prior to transfusion. (Of note, if radiation is applied to this drug, the level of potassium in the

	supernatant is increased during storage compared to non-irradiated preparations of this drug. In patients who are likely to experience hyperkalaemia, this drug should be used immediately after irradiation.)
Precautions Concerning Dosage and Administration (newly added)	Irradiation: Radiation at 15 to 50 Gy should be applied to this drug prior to transfusion.
Adverse Reactions and Infections Clinically Significant Adverse Reactions and Infections	GVHD: Cases of pyrexia and erythema that developed 1 to 2 weeks after transfusion of this drug, followed by death from GVHD accompanied by diarrhoea, hepatic impairment, granulocytopenia, etc. have been reported.

12 Human blood preparations

Frozen-thawed human red blood cells (non-irradiated preparations)

Brand name	Frozen Thawed Red Cells, Leukocytes Reduced, NISSEKI (FTRC-LR) (Japanese Red Cross Society)
[Under Old instructions]	
Warnings	The possibility of developing GVHD (graft versus host disease) due to the use of this drug cannot be ruled out. Radiation at 15 to 50 Gy should be applied to this drug prior to transfusion.
Precautions Concerning Dosage and Administration (newly added)	Irradiation: Radiation at 15 to 50 Gy should be applied to this drug prior to transfusion.
Adverse Reactions and Infections Clinically Significant Adverse Reactions and Infections	GVHD

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 adverse drug reactions (ADRs) 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 30 November 2021)
◎: Products for which EPPV was initiated after November 1, 2021

	Nonproprietary name / Branded name	Name of the MAH	Date of EPPV initiate
◎	Enfortumab vedotin (genetical recombination) / Padcev for I.V. infusion 30 mg	Astellas Pharma Inc.	November 30, 2021
◎	Progesterone / F-meno capsules 100 mg	Fuji Pharma Co., Ltd.	November 29, 2021
◎	Avalglucosidase alfa (genetical recombination) / Nexviazyme for I.V. Infusion 100 mg	Sanofi K.K.	November 26, 2021
◎	Tucidinostat[*1] / Hiyasta tablets 10 mg	Huya Japan G.K.	November 25, 2021
◎	Empagliflozin[*2] / Jardiance Tablets 10 mg	Boehringer Ingelheim Japan, Inc.	November 25, 2021
◎	Anifrolumab (genetical recombination) / Saphnelo for I.V. infusion 300 mg	AstraZeneca K.K.	November 25, 2021
◎	Relebactam hydrate/imipenem hydrate/cilastatin sodium / Recarbrio Combination for Intravenous Drip Infusion	MSD K.K.	November 9, 2021
◎	Casirivimab (genetical recombination), Imdevimab (genetical recombination) / Ronapreve Injection Set 300, 1332	Chugai Pharmaceutical Co., Ltd.	November 5, 2021
	Tucidinostat / Hiyasta tablets 10 mg	Huya Japan G.K.	October 20, 2021
	Follitropin delta (genetical recombination) / Rekovelle Pen for S.C. Injection 12 μg, 36 μg, 72 μg	Ferring Pharmaceuticals Co., Ltd.	October 1, 2021
	Sotrovimab (genetical recombination) / Xevudy for Intravenous Injection 500 mg	GlaxoSmithKline K.K.	September 29, 2021
	L-Lysine hydrochloride, L-arginine	FUJIFILM Toyama	September 29,

Nonproprietary name Branded name	Name of the MAH	Date of EPPV initiate
hydrochloride Lysakare Injection	Chemical Co., Ltd.	2021
Lutetium (^{177}Lu) hepato Lutathera Injection	FUJIFILM Toyama Chemical Co., Ltd.	September 29, 2021
Midazolam Midafresa Injection 0.1%	Alfresa Pharma Corporation	September 27, 2021
Rituximab (genetical recombination) [*3] Rituxan Intravenous Infusion 100 mg, 500 mg	Zenyaku Kogyo Co., Ltd.	September 27, 2021
Sacubitril valsartan sodium hydrate[*4] Entresto Tablets 100 mg, 200 mg	Novartis Pharma K.K.	September 27, 2021
Sirolimus[*5] Rapalimus Tablets 1 mg	Nobelpharma Co., Ltd.	September 27, 2021
Ibrutinib[*6] Imbruvica Capsules 140 mg	Janssen Pharmaceutical K.K.	September 27, 2021
Secukinumab (genetical recombination) [1] Cosentyx for s.c. injection 150 mg syringe [2] Cosentyx for s.c. injection 150 mg pen [3] Cosentyx for s.c. injection 75 mg syringe	Novartis Pharma K.K.	September 27, 2021
Dinutuximab (genetical recombination) Unituxin I.V. injection 17.5 mg/5 mL	Ohara Pharmaceutical Co., Ltd.	September 22, 2021
Imeglimin hydrochloride Twymeeg Tablets 500 mg	Sumitomo Dainippon Pharma Co., Ltd.	September 16 2021
Vericiguat Verquvo tablets 2.5 mg, 5 mg, 10 mg	Bayer Yakuhin Ltd.	September 15, 2021
Fremanezumab (genetical recombination) Ajovy Syringes for S.C. Injection 225 mg	Otsuka Pharmaceutical Co., Ltd.	August 30, 2021
Givosiran sodium Givlaari Subcutaneous Injection 189 mg	Alnylam Japan K.K.	August 30, 2021
Upadacitinib hydrate[*7] Rinvoq Tablets 7.5 mg, 15 mg	AbbVie GK	August 25, 2021
Dapagliflozin propylene glycolate hydrate[*8] Forxiga 5 mg, 10 mg tablets	AstraZeneca K.K.	August 25, 2021
Selexipag[*9] Uptravi Tablets 0.2 mg, 0.4 mg	Nippon Shinyaku Co., Ltd.	August 25, 2021
Fentanyl citrate[*10] Fentos Tapes 0.5 mg, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg	Hisamitsu Pharmaceutical Co., Inc.	August 25, 2021
Upacicalcet sodium hydrate Upasita IV Injection Syringe for Dialysis 25 μg, 50 μg, 100 μg, 150 μg, 200 μg, 250 μg, 300 μg	Sanwa Kagaku Kenkyusho Co., Ltd.	August 20, 2021
Teduglutide (genetical recombination) Revestive 3.8 mg for S.C. Injection	Takeda Pharmaceutical Company Limited.	August 18, 2021
COVID-19 (SARS-CoV-2) Vaccine (recombinant chimpanzee adenovirus vector)	AstraZeneca K.K.	August 16, 2021

Nonproprietary name / Branded name	Name of the MAH	Date of EPPV initiate
Vaxzevria Intramuscular Injection		
Erenumab (genetical recombination) / Aimovig Subcutaneous injection Pens 70 mg	Amgen K.K.	August 12, 2021
Risdiplam / Evrysdi Dry Syrup 60 mg	Chugai Pharmaceutical Co., Ltd.	August 12, 2021
Tazemetostat hydrobromide / Tazverik tablets 200 mg	Eisai Co., Ltd.	August 16, 2021
Larotrectinib sulfate / Vitrakvi oral solution 20 mg/mL	Bayer Yakuhin Ltd.	August 6, 2021
Simoctocog alfa (genetical recombination) / Nuwiq For I.V. Injection 250, 500, 1000, 2000, 2500, 3000, 4000	Fujimoto Pharmaceutical Corporation	August 2, 2021
Lyophilized human alpha1-proteinase inhibitor concentrate / Lynspad for Intravenous Infusion 1000 mg	Grifols Therapeutics LLC.	July 27, 2021
Casirivimab (genetical recombination), Imdevimab（genetical recombination） / Ronapreve for Intravenous Infusion Set 300, 1332	Chugai Pharmaceutical Co., Ltd.	July 22, 2021
Rivaroxaban*11 / Xarelto dry syrup for pediatric 51.7 mg, 103.4 mg	Bayer Yakuhin Ltd.	July 12. 2021
Amikacin sulfate / Arikayce (amikacin liposome inhalation suspension) 590 mg/8.4 mL	Insmed Incorporated.	July 7, 2021
Larotrectinib sulfate / Vitrakvi capsules 25 mg, 100 mg	Bayer Yakuhin Ltd.	July 7, 2021
Osilodrostat phosphate / Isturisa tablets 1 mg, 5 mg	Recordati Rare Diseases Japan KK	June 30, 2021
Incobotulinumtoxin A*12 / Xeomin 50 units/100 units/200 units for Intramuscular injection	Teijin Pharma Limited.	June 23, 2021
Pemigatinib / Pemazyre Tablets 4.5 mg	Incyte Biosciences Japan G.K.	June 1, 2021
Inebilizumab (genetical recombination) / Uplizna for Intravenous Infusion 100 mg	Mitsubishi Tanabe Pharma Corporation	June 1, 2021

*1 Relapsed or refractory peripheral T-cell lymphoma

*2 Chronic heart failure (only in patients who are receiving standard of care for chronic heart failure)

*3 Systemic scleroderma

*4 Hypertension

*5 Refractory lymphatic diseases (lymphangioma (lymphatic malformation), lymphangiomatosis, Gorham's disease, lymphangiectasia)

*6 Chronic graft versus host disease after haematopoietic stem cell transplantation (when steroids are not sufficiently effective)

*7 Atopic dermatitis that has not responded adequately to conventional treatments

*8 Chronic kidney disease

*9 Chronic thromboembolic pulmonary hypertension inoperable or persistent/recurrent after interventional treatment

*10 Pain relief in cancers accompanied by moderate to severe pain difficult to treat with non-opioid analgesics (limited to use as a switch from other opioid analgesics)

*11 Treatment and reduction in the risk of recurrence of venous thromboembolism

*12 Leg spasm