Pharmaceuticals and Medical Devices Safety Information

No. 412 August 2024

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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) web page (https://www.pmda.go.jp/english/safety/info-services/drugs/medical-safety-information/0002.html) and on the MHLW website (https://www.mhlw.go.jp/, only in Japanese).

Available information is listed here

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

The PMDA Medi-navi is an e-mail mailing list service that serves to provide essential safety information released by the MHLW and PMDA. Subscribing to the Medi-navi will allow you to receive this information on the day of its release.
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Pharmaceuticals and Medical Devices Safety Information

No. 412 August 2024

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

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

If healthcare professionals such as physicians, dentists, and pharmacists detect adverse reactions, infections, or malfunctions associated with drugs, medical devices, or regenerative medical products, please report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As healthcare professionals, drugstore and pharmacy personnel are also required to report adverse reactions, etc.

Please utilize the Report Reception Site for reporting.
(This service is available only in Japanese.)

https://www.pmda.go.jp/safety/reports/hcp/0002.html

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.

Abbreviations

ADR	Adverse Drug Reaction
CI	Confidence Interval
CNS	Central Nervous System
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal Year
GAD	General Affairs Division
HPB	Health Policy Bureau
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
MSI	Microsatellite Instability
MSPO	Office of Medical Safety Promotion
NYHA	New York Heart Association
PMDA	Pharmaceuticals and Medical Devices Agency
PSB	Pharmaceutical Safety Bureau
PSD	Pharmaceutical Safety Division
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
TEN	Toxic Epidermal Necrolysis

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How to Start and Proceed With Improving Polypharmacy Among the Elderly in Regions

1. Introduction

In association with the growth of aging population, concomitant administration of multiple drugs tends to cause safety problems due to physiological change by age and treatment of multiple comorbidities. The 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 considerations of the matters necessary to secure safety of drug therapy in the elderly.

So far, the Study Group has compiled and disseminated “Guidance on Appropriate Medication for Elderly Patients (general),” “Guidance of Appropriate Medication for Elderly Patients [particular (by recuperation environment)],” and “How to Start and Proceed With Improving Polypharmacy Among the Elderly in Hospitals” (HPB/GAD/MSPO 0331 No. 1 and PSEHB/PSD 0331 No. 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 March 31, 2021).

Following discussions in the Study Group, the MHLW has recently revised “How to Start and Proceed With Improving Polypharmacy Among the Elderly in Hospitals” (hereinafter referred to as the “hospital version of written operational procedures”) including a collection of example forms and the Attached Table 3/Table 4 of “Guidance on Appropriate Medication for Elderly Patients (general).” In addition, the MHLW has newly compiled “How to Start and Proceed With Improving Polypharmacy Among the Elderly in Regions” (hereinafter referred to as the “regional version of written operational procedures”) (PSB/PSD 0722 No. 1 by the Director of the Pharmaceutical Safety Division, Pharmaceutical Safety Bureau, MHLW, dated July 22, 2024).

In this section, the Study Group’s efforts until now as well as the operational procedures for polypharmacy measures in regions are introduced.

2. Past efforts

The Study Group compiled “Guidance on Appropriate Medication for Elderly Patients (general)” in 2017 as the basic considerations for practicing better drug therapy that takes into account the characteristics of elderly people, and “Guidance of Appropriate Medication for Elderly Patients [particular (by recuperation environment)]” in 2018 as the considerations for the medical treatment environment of each patient. In 2021, the Study Group compiled the hospital version of written operational procedures not only to have hospitals, which were just launching polypharmacy measures, use them as a start-up tool to solve the problems they might face but also to have hospitals, which had already made some progress in their measures, use them as reference materials in preparing their own operational procedures and making their operations more efficient.

In fiscal year (FY) 2023, the Study Group again conducted a survey on the status of polypharmacy measures in hospitals, which had previously been conducted in FY 2019, in order to further promote the polypharmacy measures for the elderly. It also newly conducted a similar survey on a regional basis to understand the actual situation and issues, etc. regarding the polypharmacy measures. Based on the results, it compiled the following recommendations.

(1) Recommendations for polypharmacy measures in hospitals

Recommendation 1: To promote organizational polypharmacy measures through the establishment of multi-occupational teams
Recommendation 2: To promote sharing tasks from pharmacists to other professions
Recommendation 3: To raise awareness among healthcare professionals
Recommendation 4: To utilize tools to share information outside the hospital

(2) Actual situation and issues to be considered regarding polypharmacy measures in regions

Recommendation 1: To put polypharmacy measures on the agenda of regional collaborative committees
Recommendation 2: To establish a principal body that takes the initiative
Recommendation 3: To conduct awareness-raising activities in regions
Recommendation 4: To utilize tools to share information in regions

3. How to start and proceed with improving polypharmacy among the elderly in regions

The regional version of the written operational procedures has recently been compiled for use in the actual implementation of polypharmacy measures in regions, since polypharmacy measures become more practical when they are taken on a region-wide basis. The operational procedures have two major purposes. The first is to be used from the perspective of how to deal with the patients in front of you in order to solve the problems you face in the early stages of the efforts (Chapter 1). The second is to be used as reference materials for the development of regional manuals, etc. to make operations more efficient in implementing the polypharmacy measures, contributing to the promotion of the measures throughout the region (Chapter 2). The main targets of the operational procedures are physicians, dentists, and pharmacists, but they are also intended for a wider range of people involved in the polypharmacy measures. Please use these materials together with the hospital version of written operational procedures to promote polypharmacy measures throughout the region including hospitals.

* Polypharmacy measures in regions assume situations where clinics and pharmacies work together, or where principal bodies such as administration, medical care institutions, nursing care facilities, and academic experts work together on a municipal basis through collaborative committees, etc. Situations where polypharmacy measures are led by hospitals as described in “How to Start and Proceed With Improving Polypharmacy Among the Elderly in Hospitals” are not assumed here.

The contents of the operational procedures are as follows.

Chapter 1 How to start polypharmacy measures

○ Before starting polypharmacy measures

Rather than focusing only on a uniform number of drugs or types of drugs, it is necessary to start polypharmacy measures by understanding that prescriptions must be optimized in terms of ensuring safety, etc.

- To build the relationships among patients, their family members, and multi-occupational professionals
- To prepare briefing materials for patients and their family members

○ How to begin with small issues

- To start small
- To utilize already existing arrangements and tools
- To encourage patients to decide a key person to adjust polypharmacy

Table Glossary on how to start and proceed with improving polypharmacy among the elderly in regions

Term	Description
Person who assists drug adjustment (drug adjustment assistant)	A person who has a certain level of knowledge about polypharmacy measures, who understands the status of prescriptions and medications for individual patients in providing medical care and nursing care in the region, and who supports the relevant patients by taking responsibility for the polypharmacy issues they have and by interacting with medical institutions and pharmacies involved with the patients (suggesting changes in prescriptions, etc.) in order to ensure that appropriate prescriptions are given and medications are taken properly according to the patients' conditions. * A term used for convenience in this document * There is no obligation to appoint such personnel in the administrative system, etc.
Regional polypharmacy coordinator	A person who works with those involved in medical and nursing care in the region with their understanding, who plays a central role in reviewing the policy on polypharmacy measures in the entire region, and who leads the regional polypharmacy measures. * A term used for convenience in this document * There is no obligation to appoint such personnel in the administrative system, etc.

○ Challenges and countermeasures for starting polypharmacy measures

It provides countermeasures to challenges, such as "insufficient multi-occupational cooperation," "being unable to understand patients' medications in an integrated manner," "necessity to efficiently identify polypharmacy patients," "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 feed back the revised prescription details to primary physicians," and "being too understaffed to make time to be actively involved in the regional polypharmacy measures."

Chapter 2 How to proceed with polypharmacy measures

○ Setting up a system for polypharmacy measures

- To confirm the concept of polypharmacy
- To identify the purposes of polypharmacy measures
- To prepare related materials
- To decide who will be in charge of promoting polypharmacy measures
- To have local governments and insurers get involved in polypharmacy measures
- To develop a cooperation structure with medical/nursing care professionals, etc., who are responsible for the comprehensive community care system
- To promote polypharmacy measures using information technology
- To consider the costs

○ Implementation of polypharmacy measures

- To review the overall policy on polypharmacy measures in the region at collaborative committees
- To understand the current situation of the region
- To improve understanding among the regional population
- To gain understanding of regional medical/nursing care professionals, etc.
- To conduct awareness-raising activities in regions
- To monitor results of polypharmacy measures

○ Example of case-specific implementation of polypharmacy measures

It provides examples of how situations such as the following can be handled: Patients receiving outpatient or in-home medical care; patients discharged from medical institutions; patients residing in care and health service facilities for the aged; how to work with local governments and insurers; and how to have cooperation across multiple professions.

○ 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 review, and monitoring of patients' conditions after prescription revision) are contained.

4. Closing remark

"How to Start and Proceed With Improving Polypharmacy Among the Elderly in Regions," "How to Start and Proceed With Improving Polypharmacy Among the Elderly in Hospitals," "Guidance on Appropriate Medication for Elderly Patients (general)," and "Guidance of Appropriate Medication for Elderly Patients [particular (by recuperation environment)]" introduced here are available on the website of the MHLW. Healthcare professionals are encouraged to read through the website and to use the information for the polypharmacy measures in hospitals and regions.

[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 (in Japanese)
  https://www.pmda.go.jp/files/000232249.pdf (in 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)
- Report on the FY 2019 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)
- "How to Start and Proceed With Improving Polypharmacy Among the Elderly in Hospitals" and "How to Start and Proceed With Improving Polypharmacy Among the Elderly in Regions"
  (PSB/PSD 0722 No. 1, dated July 22, 2024)
  https://www.mhlw.go.jp/content/11120000/001277264.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)
- Report on the Survey on the Project to Promote the Appropriate Medication for Elderly Patients and Report on the Reviews of Guidance and Written Operational Procedures, etc.
  (Material 1, the 18th Study Group on the Appropriate Medication for Elderly Patients on June 21, 2024)
  https://www.mhlw.go.jp/content/11125000/001265396.pdf (only in Japanese)
- Pharmaceuticals and Medical Devices Safety Information No. 389 How to Start and Proceed With Improving Polypharmacy Among the Elderly in Hospitals
  https://www.mhlw.go.jp/content/11120000/000878166.pdf (in Japanese)
  https://www.pmda.go.jp/files/000244514.pdf (in English)

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Important Safety Information

Regarding the revision of the PRECAUTIONS of package inserts of drugs in accordance with the Notification dated July 17, 2024 this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 Epoprostenol sodium

Brand name (name of company)	Flolan for Injection 0.5 mg, 1.5 mg (GlaxoSmithKline K.K.), and the others
Therapeutic category	Other cardiovascular agents
Indications	Pulmonary arterial hypertension

RECAUTIONS (Revised language is underlined.)

11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Ascites If ascites is observed, the possibility that it may be due to this drug or other causes (right heart failure, liver disorder, etc.) should be considered. If this drug is suspected to be the cause after evaluating possible causes for ascites, appropriate measures should be taken such as dose reduction or discontinuation of this drug.
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports Cases involving ascites reported in Japan: 3 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 140 Japanese market launch: 0.5 mg: April 1999 1.5 mg: July 2001

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Female Unknown	Pulmonary arterial hypertension (unknown)	75 ng/kg/min unknown ↓ 66 ng/kg/min unknown	**Ascites, high output cardiac failure, pulmonary congestion**	
				Before start of administration	The patient was diagnosed with idiopathic pulmonary arterial hypertension in her 20s. Acute pulmonary vasoreactivity testing was negative. Treatment with sildenafil citrate, bosentan hydrate, and a diuretic was initiated.
				3 years after start of treatment	The patient was diagnosed with Class IV on the New York Heart Association (NYHA) classification.
				Day 1 of administration of epoprostenol sodium	Administration of epoprostenol sodium was initiated.
				2 years after start of administration of epoprostenol sodium	After the start of administration of epoprostenol sodium, the dose was gradually increased, and the NYHA classification improved from Class IV to Class III in 2 years.
				Date unknown (day of onset)	Ascites developed. Due to ascites retention over several months, the patient was admitted to the hospital. The ascites was transudative. Hypoproteinaemia, portal hypertension, lymphoma, and lymphatic obstruction were ruled out. High output cardiac failure and pulmonary congestion developed. A high-dose diuretic was administered simultaneously with drip infusion of albumin, and abdominal paracentesis was performed. However, ascites rapidly accumulated again after drainage. The measurement results of the right cardiac catheterization revealed no progression of pulmonary arterial hypertension, suggesting the possibility of high output cardiac failure. The dose of epoprostenol sodium was reduced from 75 ng/kg/min to 66 ng/kg/min in a month. After the dose reduction of epoprostenol sodium, the massive ascites gradually decreased, and pulmonary congestion improved.
				Date unknown	The outcome of ascites was reported as resolved. Eventually, ascites completely disappeared with the improvement of the NYHA classification to Class III. Thereafter, no recurrence of ascites or aggravation of right heart failure was observed. The outcome of pulmonary congestion was also reported as resolved.
				Approximately 2 years after dose reduction	The dose reduction of epoprostenol sodium did not result in aggravation of the underlying pulmonary arterial hypertension.

Laboratory test value (right cardiac catheterisation)

	Before administration of epoprostenol sodium	Approximately 2 years after start of administration	Approximately 2 years after dose reduction
Pulmonary vascular resistance (dynes· sec· cm^{-5})	855	217	160
Mean pulmonary arterial pressure (mmHg)	64	35	33
Cardiac output [Fick method] (L/min)	-	9.9	-
Cardiac index [Fick method] ($L/min/m^2$)	-	6.8	-

Mean right atrial pressure (mmHg)	-	8	-
Pulmonary arterial wedge pressure (mmHg)	-	10	-
Mixed venous blood saturation (%)	-	81.5	-

Suspected concomitant drugs: None
Concomitant drugs: Sildenafil citrate, bosentan hydrate, diuretic

2 [1] Nivolumab (genetical recombination)
[2] Ipilimumab (genetical recombination)

Brand name (name of company)	[1] Opdivo I.V. Infusion 20 mg, 100 mg, 120 mg, 240 mg (Ono Pharmaceutical Co., Ltd.) [2] Yervoy Injection 20 mg, 50 mg (Bristol-Myers Squibb K.K.)
Therapeutic category	Other antitumor agents
Indications	[1] •Malignant melanoma •Unresectable, advanced or recurrent non-small cell lung cancer •Neoadjuvant therapy for non-small cell lung cancer •Radically unresectable or metastatic renal cell carcinoma •Relapsed or refractory classical Hodgkin lymphoma •Recurrent or metastatic head and neck cancer •Unresectable, advanced or recurrent gastric cancer •Unresectable, advanced or recurrent malignant pleural mesothelioma •Malignant mesothelioma (excluding malignant pleural mesothelioma) •Unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer that has progressed after chemotherapy •Radically unresectable, advanced or recurrent oesophageal carcinoma •Postoperative adjuvant therapy for oesophageal carcinoma •Carcinoma of unknown primary •Postoperative adjuvant therapy for urothelial carcinoma •Radically unresectable, advanced or recurrent malignant epithelial tumor [2] •Radically unresectable malignant melanoma •Radically unresectable or metastatic renal cell carcinoma •Unresectable, advanced or recurrent microsatellite instability high (MSI-High) colorectal cancer that has progressed after chemotherapy •Unresectable, advanced or recurrent non-small cell lung cancer •Unresectable, advanced or recurrent malignant pleural mesothelioma •Radically unresectable advanced or recurrent oesophageal carcinoma

PRECAUTIONS (Revised language is underlined.)

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Encephalitis, meningitis<u>, myelitis</u>
Reference information	Number of cases for which information on cerebrospinal fluid tests, blood cultures, or PCR testing, in addition to information on the results of spinal MRI examinations, is available within the case report form among those collected in the PMDA's database for adverse drug

reactions, etc. report
Cases involving myelitis reported in Japan and overseas:
[1] Cases involving myelitis reported in Japan: 1 (No patient mortalities)
Cases involving myelitis reported in overseas: 16 (No patient mortalities)
[2] Cases involving myelitis reported in Japan: 1 (No patient mortalities)
Cases involving myelitis reported in overseas: 10 (No patient mortalities)

Number of patients using the drug as estimated by the MAH during the previous 1-year period: [1] Approximately 32,700
[2] Approximately 10,937
Japanese market launch:
[1] Opdivo I.V. Infusion 20 mg, 100 mg: September 2014
Opdivo I.V. Infusion 240 mg: November 2018
Opdivo I.V. Infusion 120 mg: November 2020
[2] Yervoy Injection 50 mg: August 2015
Yervoy Injection 20 mg: November 2021

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Male 60s	Recurrent non-small cell lung cancer (metastases to lymph nodes, malignant pleural effusion, hyperuricaemia)	360 mg 2 courses at 27 days interval	**Immune-mediated myelitis** The patient had a history of smoking.	
				Day 1 of administration	Administration of nivolumab (genetical recombination) (360 mg), ipilimumab (genetical recombination) (60 mg), cisplatin (128 mg), and pemetrexed sodium hydrate (850 mg) was started as a combination therapy for PS1 unresectable advanced/recurrent non-small cell lung cancer (lung adenocarcinoma, stage IV, PD-L1: less than 1%).
				27 days after administration	Nivolumab, cisplatin, and pemetrexed sodium hydrate were administered.
				41 days after administration	Dysuria appeared.
				45 days after administration	Urinary incontinence and motor paralysis of the right lower limb appeared.
				46 days after administration	The patient complained of motor paralysis of the right lower limb and bladder dysfunction, and he was urgently admitted to the hospital.
				47 days after administration (day of discontinuation)	Motor paralysis and sensory paralysis of both upper and lower limbs appeared. A contrast-enhanced MRI revealed myelitis from the cervical to thoracic spine levels. Metastases to the central nervous system or encephalitis were not observed. He was diagnosed with immune-mediated myelitis. Administration of nivolumab and ipilimumab was discontinued. [MRI examinations] Hyperintensity in the cervical and upper thoracic spinal cords (C3/4-7, Th1, 3)
				1 day after discontinuation	A cerebrospinal fluid test showed increased cell counts, but they were not malignant cells. [Cerebrospinal fluid test] Albumin: 31.1 mg/dL, cell count: 13/μL, chloride: 120 mmol/L, glucose: 59 mg/dL, protein: 57 mg/dL, red blood cell count: 0/μL, mononuclear cell: 13/μL, polymorphonuclear cell: 0/μL, oligoclonal band (-) [Other laboratory tests] Anti-AQP4 antibody (-), sIL-2 receptor: 1277.2 U/mL, herpes simplex test (-)
				2 days after discontinuation	Administration of methylprednisolone sodium succinate (1 g) was started as steroid pulse therapy.
				5 days after discontinuation	Administration of prednisolone (60 mg) was started. Paralysis of the upper and lower limbs worsened.
				9 days after discontinuation	Administration of methylprednisolone sodium succinate (1 g) was started as steroid pulse therapy.
				12 days after discontinuation	Administration of prednisolone (60 mg) was started. Paralysis of the upper and lower limbs showed a tendency to improve.
				23 days after discontinuation	MRI examinations showed a tendency toward improvement in immune-mediated myelitis.
				26 days after discontinuation	The dose of prednisolone was reduced to 50 mg. The dose of prednisolone was tapered subsequently.

				54 days after discontinuation	The patient was discharged from the hospital.
				Date unknown	A CT scan revealed progression of carcinomatous pleurisy and metastases to lymph nodes. Administration of sotorasib (960 mg) was started in combination with prednisolone (5 mg).
				186 days after discontinuation	Immune-mediated myelitis resolved with sequelae (impaired urination). Administration of prednisolone was terminated.
	Suspected concomitant drugs: Ipilimumab (genetical recombination) Concomitant drugs: Cisplatin, pemetrexed sodium hydrate, sotorasib				

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
2	Male 60s	Recurrent non-small cell lung cancer (metastases to lymph nodes, malignant pleural effusion, hyperuricaemia)	60 mg once daily for 1 day ↓ Discontinuation	**Immune-mediated myelitis** The patient had a history of smoking.	
				Day 1 of administration (day of termination)	Administration of ipilimumab (60 mg), nivolumab (360 mg), cisplatin (128 mg), and pemetrexed sodium hydrate (850 mg) was started as a combination therapy for PS1 unresectable advanced/recurrent non-small cell lung cancer (lung adenocarcinoma, stage IV, PD-L1: less than 1%).
				27 days after termination	Nivolumab, cisplatin, and pemetrexed sodium hydrate were administered.
				41 days after termination	Dysuria appeared.
				45 days after termination	Urinary incontinence and motor paralysis of the right lower limb appeared.
				46 days after termination	The patient complained of motor paralysis of the right lower limb and bladder dysfunction and he was urgently admitted to the hospital.
				47 days after termination	Motor paralysis and sensory paralysis of both upper and lower limbs appeared. A contrast-enhanced MRI revealed myelitis from the cervical to thoracic spine levels. Metastases to the central nervous system or encephalitis were not observed. He was diagnosed with immune-mediated myelitis. Administration of ipilimumab and nivolumab was discontinued. [MRI examinations] Hyperintensity in the cervical and upper thoracic spinal cords (C3, 4-7, Th1, 3)
				48 days after termination	A cerebrospinal fluid test showed increased cell counts, but they were not malignant cells. [Cerebrospinal fluid test] Albumin: 31.1 mg/dL, cell count: 13/μL, chloride: 120 mmol/L, glucose: 59 mg/dL, protein: 57 mg/dL, red blood cell count: 0/μL, mononuclear cell: 13/μL, polymorphonuclear cell: 0/μL, oligoclonal band (-) [Other laboratory tests] Anti-AQP4 antibody (-), sIL-2 receptor: 1277.2 U/mL, herpes simplex test (-)
				49 days after termination	Administration of methylprednisolone sodium succinate (1 g) was started as steroid pulse therapy.
				52 days after termination	Administration of prednisolone (60 mg) was started. Paralysis of the upper and lower limbs worsened.
				56 days after termination	Administration of methylprednisolone sodium succinate (1 g) was started as steroid pulse therapy.
				59 days after termination	Administration of prednisolone (60 mg) was started. Paralysis of the upper and lower limbs showed a tendency to improve.
				70 days after termination	MRI examinations showed a tendency toward improvement in immune-mediated myelitis.
				73 days after termination	The dose of prednisolone was reduced to 50 mg. The dose of prednisolone was tapered subsequently.
				101 days after termination	The patient was discharged from the hospital.

				Date unknown	A CT scan revealed progression of carcinomatous pleurisy and metastases to lymph nodes. Administration of sotorasib (960 mg) was started in combination with prednisolone (5 mg).
				233 days after termination	Immune-mediated myelitis resolved with sequelae (impaired urination). Administration of prednisolone was terminated.
	Suspected concomitant drugs: Nivolumab (genetical recombination) Concomitant drugs: Cisplatin, pemetrexed sodium hydrate, sotorasib				

3 Tirabrutinib hydrochloride

Brand name (name of company)	Velexbru Tablets 80 mg (Ono Pharmaceutical Co., Ltd.)
Therapeutic category	Other antitumor agents
Indications	·Recurrent or refractory primary central nervous system lymphoma ·Waldenström's macroglobulinaemia and lymphoplasmacytic lymphoma

PRECAUTIONS (Revised language is underlined.)

7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION

If adverse reactions occur following administration of this drug, this drug should be discontinued temporarily or permanently, or the dose should be reduced by referring to the following criteria.
A guide for temporary/permanent drug discontinuation or dose reduction in the event of adverse reactions

Adverse reactions*		Treatment
Skin disorders	Grade 2	Antihistamines, corticosteroids, etc. should be administered. If the patient recovers from adverse reactions, administration of this drug should be continued. If the patient does not recover from adverse reactions, administration of this drug should be continued by reducing the dose by one level or administration of this drug should be temporarily discontinued.
	Grade 3 or higher	Antihistamines, corticosteroids, etc. should be administered, and administration of this drug should be temporarily discontinued until adverse reactions recover to grade 2 or lower. After the recovery, administration can be resumed by reducing the dose by one level.
	Oculomucocutaneous syndrome (Stevens-Johnson syndrome) or toxic epidermal necrolysis (TEN)	Administration should be permanently discontinued.

* Grade should be in accordance with NCI-CTCAE v4.0.

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions

Severe skin disorders
Severe skin disorders such as toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme, or toxic skin eruption may occur.

Reference information

Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database

for adverse drug reactions, etc. reports
Cases involving TEN reported in Japan: 4 (No patient mortalities)
Cases involving oculomucocutaneous syndrome reported in Japan: 10 (No patient mortalities)
Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 1,062
Japanese market launch: May 2020

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Male 50s	Lymphoplasmacytoid lymphoma/ immunocytoma (nephrotic syndrome)	480 mg for 31 days ↓ discontinuation	**Stevens-Johnson syndrome** The patient had a history of knee fracture and drinking.	
				Date unknown	Oral prednisolone (12.5 mg/day) had been administered for nephrotic syndrome.
				Day 1 of administration	Administration of tirabrutinib hydrochloride was initiated for the treatment of Waldenström's macroglobulinaemia and lymphoplasmacytic lymphoma.
				Day 31 of administration (day of discontinuation)	Administration of tirabrutinib hydrochloride was discontinued.
				1 day after discontinuation	Skin eruption and bulbar conjunctiva hyperaemia were observed. Administration of epinastine hydrochloride ophthalmic solution was initiated. On the same day, the patient visited the hospital at night. Stevens-Johnson syndrome was observed. Macular redness was sporadically noted in the body trunk and the neck, and mild itching was noted. He had no stomatitis. The patient's body temperature was 36.1°C. Administration of olopatadine hydrochloride (dose unknown) was initiated.
				3 days after discontinuation	Aggravated skin rash and pyrexia (38.2°C) were noted. Bilateral conjunctival hyperemia, pharynx redness, upper and lower lip swelling, and aphtha in the oral cavity were noted. Papules on the front and back of the trunk and extremities with a tendency to fuse in some places, and ruptures of blisters on the anterior surface of the trunk were noted. The dose of oral prednisolone was increased to 30mg/day.
				4 days after discontinuation	Aggravation of skin eruption was observed. Multiple raised erythemas and papules developed over the entire body, and some parts were target lesions with a tendency to fuse. A rupture of the membrane of blisters was noted in the lower limbs. The central body trunk was slightly discolored and planarized. Blisters and erosions were observed in some parts, and Nikolsky's sign was observed in erythemas (10% of the whole body area). Tenderness was noted. The patient had no spontaneous pain. Erosion was noted in the glans and the scrotum. No changes were seen in the conjunctiva and enanthem of the lips. The patient's body temperature was 37.9°C. The patient was urgently admitted to the hospital. Administration of intravenous infusion of prednisolone (60 mg/day) was initiated.
				5 days after discontinuation	Bilateral ciliary hyperaemia and a slight opacity due to an immune reaction in the limbus were noted in his eyes. No corneal epithelium disorder or anterior chamber inflammation was noted. Neogenesis of blisters and spontaneous pain were noted in the lower extremities. The patient's body temperature was 37.3°C. Administration of intravenous infusion of methylprednisolone sodium succinate (1000 mg/day) was initiated.

					[Skin biopsy] Skin biopsy was conducted on the target lesion erythema on the left dorsum pedis. Humoral degeneration of epidermal-dermal junction was noted. Lymphocyte infiltration and spongiosis were observed in the epidermis, and multiple individual cell necroses were observed in the surrounding area. Perivascular lymphocytic infiltrates were noted in the superficial dermal layer. Eosinophilic infiltration was not confirmed. Erythema multiforme was suspected. No malignant findings were observed.
				6 days after discontinuation	Although the skin eruption of the central body trunk tended to be discolored and fuse, erythema of the face and upper and lower extremities tended to expand, and neogenesis of blisters was observed. The patient's body temperature was 36.8°C.
				10 days after discontinuation	Neogenesis of erosion and erythema continued. Therefore, administration of oral prednisolone (60 mg/day) and intravenous infusion of immunoglobulin were initiated.
				15 days after discontinuation	Neogenesis of erythema stabilized, and Nikolsky's sign became negative. Therefore, the dose of oral prednisolone was reduced to 50 mg/day.
				28 days after discontinuation	No flare-up of skin redness was noted, and the dose of oral prednisolone was reduced to 30 mg/day. Stevens-Johnson syndrome remitted.

Laboratory test value

	19 days before administra-tion	Day 1 of administra-tion	Day 17 of administra-tion	3 days after discontinu-ation	4 days after discontinu-ation	5 days after discontinu-ation	6 days after discontinu-ation	28 days after discontinu-ation
C-reactive protein (mg/dL)	0.01	0.02	0.01	0.77	2.01	1.39	0.85	0.05
Aspartate aminotransferase (U/L)	11	15	12	19	25	23	18	28
Alanine aminotransferase (U/L)	25	16	10	13	19	18	21	49
Haemoglobin (g/dL)	13.6	14.2	13.1	13.7	13.5	13.9	13.3	11.3
Platelet count (10^4/μL)	30.1	38.4	33.6	28.4	23.2	26.9	26.7	27.3
Blood alkaline phosphatase (U/L)	44	46	40	42	43	38	40	71
Blood creatinine (mg/dL)	0.77	0.74	0.84	0.83	0.76	0.68	0.71	0.61
Blood bilirubin (mg/dL)	0.6	0.8	1.1	0.9	0.5	0.5	0.5	0.8
Blood lactate dehydrogenase (U/L)	106	113	107	186	216	227	155	184
Urea nitrogen (mg/dL)	16	14	17	14	18	17	26	21
WBC count (10^3/μL)	7.2	7.5	9.2	10.0	9.0	9.4	10.5	10.2
Neutrophil count (10^3/μL)	4.46	6.68	6.53	9.4	8.37	6.86	9.03	8.87
Lymphocyte count (10^3/μL)	2.52	0.75	2.21	0.3	0.54	1.79	1.05	1.12
Eosinophil count (10^3/μL)	0	0	0	0	0	0	0	0

Concomitant drugs: Prednisolone, esomeprazole magnesium hydrate, sulfamethoxazole/trimethoprim, eldecalcitol

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
2	Female 80s	Primary central nervous system lymphoma (none)	480 mg for 28 days ↓ discontinuation	**Stevens-Johnson syndrome** Cataract, acute appendicitis	
				Day 1 of administration	Administration of tirabrutinib hydrochloride was initiated for treatment of relapsed or refractory primary central nervous system (CNS) lymphoma (primary tumor: Cerebrum (right frontal lobe), DLBCL (Non-GCB)).
				Day 27 of administration:	Stevens-Johnson syndrome (Grade 3) was observed. Skin eruption with itching appeared in the body trunk/both lower legs. Administration of bilastine was initiated.
				Day 28 of administration (day of discontinuation)	Tirabrutinib hydrochloride was discontinued.
				3 days after discontinuation	Less than 10% of the body surface area was affected by lesions, including erythema in the body trunk, both thighs, and bilateral forearms. No enanthema was observed. Administration of topical betamethasone butyrate propionate and fexofenadine hydrochloride (120 mg×2/days) was initiated.
				7 days after discontinuation	Administration of ceftriaxone sodium hydrate (2000 mg/day) was initiated.
				8 days after discontinuation	The patient subsequently developed pyrexia (38.8°C), and she visited the hospital. Expansion of erythema, blistering and epidermal detachment in part of the side lumbar region, oral mucosal eruption, and lip erosion were noted. She was admitted to the hospital, and administration of intravenous infusion of methylprednisolone sodium succinate (1000 mg/day) was initiated.
				11 days of discontinuation	Erythema showed a tendency to fade. The patient's body temperature was 36.4°C. Oral administration of prednisolone (30 mg× 2/day) was initiated.
				15 days after discontinuation	Erythema showed a tendency to fade. The patient's body temperature was 36.8°C.
				16 days after discontinuation	The dose of oral prednisolone was reduced to 25 mg × 2/day.
				18 days after discontinuation	Erythema showed a tendency to fade, and epithelialization of the erosion area was noted. The patient's body temperature was 36.2°C.
				19 days after discontinuation	The dose of oral prednisolone was reduced to 20 mg × 2/day.
				21 days after discontinuation	The dose of oral prednisolone was reduced to 15 mg/day.
				22 days after discontinuation	Erythema improved. The patient's body temperature was 36.7°C.
				23 days after discontinuation	The dose of oral prednisolone was reduced to 10 mg/day.
				25 days after discontinuation	The dose of oral prednisolone was reduced to 5 mg/day.
				28 days after discontinuation	Stevens-Johnson syndrome resolved.
	Concomitant drugs: None				

4 Gadobutrol

Brand name (name of company)	Gadovist iv injection 1.0 mol/L syringes 5 mL, 7.5 mL, 10 mL, Gadovist iv injection 1.0 mol/L 2 mL (Bayer Yakuhin, Ltd.)
Therapeutic category	Other diagnostic agents (except extracorporeal diagnostic medicines)
Indications	Magnetic resonance imaging of the following parts •Brain and spinal cord •Trunk and extremities

PRECAUTIONS (Revised language is underlined.)

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Shock, anaphylaxis Shock or anaphylaxis (decreased blood pressure, dyspnoea, loss of consciousness, pharyngeal/laryngeal oedema, face oedema, respiratory arrest, cardiac arrest, etc.) may occur. <u>Acute respiratory distress syndrome, pulmonary oedema</u> <u>If rapidly progressive dyspnoea, hypoxaemia, or chest X-ray abnormalities such as diffuse infiltrative shadow in both lungs are observed, appropriate measures should be taken as necessary.</u>
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) that were reported as adverse drug reaction names (PT) "acute respiratory distress syndrome," "acute pulmonary oedema," "pulmonary oedema," and "non-cardiogenic pulmonary oedema" and that included a description concerning chest imaging findings within the report among cases collected in the PMDA's database for adverse drug reactions, etc. reports is shown below. Of note, cases of pulmonary oedema associated with shock or anaphylaxis were excluded from those retrieved cases for which a causal relationship between the drug and event was reasonably possible, since it is a known event for which precautions have already been included in the package insert. Cases involving acute respiratory distress syndrome reported in Japan: 6 (No patient mortalities) Cases involving pulmonary oedema reported in Japan: 11 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 809,548 Japanese market launch: iv injection 1.0 mol/L syringes 5 mL, 7.5 mL, 10 mL: June 2015 iv injection 1.0 mol/L 2 mL: August 2018

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Female 70's	Lipoma (unknown)	6 mL Single administration	**Non-cardiogenic pulmonary oedema**	
				Day of administration	Gadobutrol 6 mL per dose was administered intravenously for diagnostic imaging (suspected neck lipoma).
				(End day of administration)	After completion of the examination, dyspnoea was noted. The oxygen saturation decreased (70 to 80%). One half of an ampoule of adrenaline (0.5 mg) was administered. A CT scan revealed a finding of pulmonary oedema. An echocardiography showed no problems in cardiac function. The patient was admitted to the hospital, and she was treated with high-flow oxygen therapy (nasal high flow) and steroids.
				6 days after administration	Non-cardiogenic pulmonary oedema was resolving. The patient was discharged from the hospital.
	Concomitant drugs: Clopidogrel sulfate, atorvastatin calcium hydrate, atenolol, vonoprazan fumarate				

3

Revisions of PRECAUTIONS (No. 352)

This section presents details of revisions to the PRECAUTIONS and brand names of drugs that have been revised in accordance with the Notifications dated July 4, July 17, 2024.

1 Vaccines

Freeze-dried smallpox vaccine prepared in cell culture

Brand name	Freeze-dried Smallpox Vaccine Prepared in Cell Culture LC16 “KMB” (KM Biologics Co., Ltd.)
(newly added)	5. PRECAUTIONS CONCERNING INDICATIONS Prior to vaccination to patients with human immunodeficiency virus infection, it should be confirmed that CD4-positive cell count is 200 cells/μL or more. There is no experience of administering this vaccine to patients with human immunodeficiency virus infection whose CD4-positive cell count is less than 200 cells/μL.
14. PRECAUTIONS CONCERNING USE (newly added)	Storage of Vaccine before Reconstitution Refrigerated Storage (1)This vaccine can be stored at 2 to 8°C for 2 years. (2)Once the vaccine is moved to refrigerated storage, it should be used without being returned to frozen storage within the expiration period and within 2 years after being moved to refrigerated storage. Storage at Room Temperature (1)This vaccine can be stored for 4 weeks at room temperature (37°C or below). (2)Once this vaccine is moved to room temperature storage, it should be used without being returned to frozen or refrigerated storage within the expiration period and within 4 weeks after being moved to room temperature storage. Storage of Vaccine after Reconstitution After reconstitution with the provided diluent, the vaccine should be used within 24 hours when it is stored at room temperature (37°C or below). When the vaccine is stored refrigerated (2 to 6°C), it should be used within one month. This vaccine does not contain preservatives. Therefore, caution should be exercised to prevent bacterial contamination properly when it is reconstituted and stored in polypropylene cryotubes, etc. after being dispensed. The vaccine solution in a vial whose stopper has been removed in a non-sterile environment should be used immediately. The solution remaining in the vial must always be disposed of without being stored again and used for the next vaccination.
Precautions Concerning Administration of the Vaccine	Before reconstituting the vaccine, the container stopper and its surroundings should be disinfected using alcohol. After that, the vaccine should be homogeneously reconstituted with 0.5 ml of provided diluent. After reconstitution, the rubber stopper should be removed by cutting the metal cap. The tip of the bifurcated needle
Administration of Vaccine	

	should be soaked in the solution, and vaccine solution appropriate for one recipient should be sucked out.
(newly added)	In cases such as mass vaccination where a large number of persons need to be inoculated consecutively, approximately more than 250 recipients can be vaccinated if the 0.5 mL of vaccine solution is prepared by reconstituting this vaccine with 0.5 mL of provided diluent and bifurcated needles for smallpox vaccination with a single collection volume of 1 ± 0.5 μL (specified value) are used.

2 Other cardiovascular agents

Epoprostenol sodium

Brand name	Flolan for Injection 0.5 mg, 1.5 mg (GlaxoSmithKline K.K.), and the others
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Ascites If ascites is observed, the possibility that it may be due to this drug or other causes (right heart failure, liver disorder, etc.) should be considered. If this drug is suspected to be the cause after evaluating possible causes for ascites, appropriate measures should be taken such as dose reduction or discontinuation of this drug.

3 Enzyme preparations

Pabinafusp alfa (genetical recombination)

Brand name	Izcargo for I.V. infusion 10 mg (JCR Pharmaceuticals Co., Ltd.)
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.5 Pregnant women**	(deleted)

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

Daprodustat

Brand name	Duvroq Tablets 1 mg, 2 mg, 4 mg, 6 mg (GlaxoSmithKline K.K.)
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc.** **(newly added)**	Patients with cardiac failure or a history of the disease Exacerbation or relapse of cardiac failure may occur. The results of subgroup analyses for patients with cardiac failure or a history of the disease, which were conducted as post-hoc analyses of overseas clinical studies, were as follows: In the clinical study in patients with chronic kidney disease on dialysis, the incidence ratio of the first hospitalization for cardiac failure was 17.6% (47/267 cases) for the daprodustat group and 12.6% (32/254 cases) for the erythropoietin stimulating agents group with a hazard ratio of 1.52 (95% CI: 0.97−2.38); in the clinical study in patients with chronic kidney disease not on dialysis, the incidence ratio was 20.4% (54/265 cases) for the daprodustat group and 13.4% (34/254 cases) for the erythropoietin stimulating agents group with a hazard ratio of 1.37 (95% CI: .89−2.11). Thus, the ratios for the daprodustat group tended to be higher in both clinical studies.

5 Other antitumor agents

[1] Ipilimumab (genetical recombination)
[2] Nivolumab (genetical recombination)

Brand name
[1]Yervoy Injection 20 mg, 50 mg (Bristol-Myers Squibb K.K.)
[2] Opdivo I.V. Infusion 20 mg, 100 mg, 120 mg, 240 mg (Ono Pharmaceutical Co., Ltd.)

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions
Encephalitis, meningitis, myelitis

6 Other antitumor agents

Tirabrutinib hydrochloride

Brand name
Velexbru Tablets 80 mg (Ono Pharmaceutical Co., Ltd.)

7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION
If adverse reactions occur following administration of this drug, this drug should be discontinued temporarily or permanently, or the dose should be reduced by referring to the following criteria.

A guide for temporary/permanent drug discontinuation or dose reduction in the event of adverse reactions

Adverse reactions*		Treatment
Skin disorders	Grade 2	Antihistamines, corticosteroids, etc. should be administered. If the patient recovers from adverse reactions, administration of this drug should be continued. If the patient does not recover from adverse reactions, administration of this drug should be continued by reducing the dose by one level or administration of this drug should be temporarily discontinued.
	Grade 3 or higher	Antihistamines, corticosteroids, etc. should be administered, and administration of this drug should be temporarily discontinued until adverse reactions recover to grade 2 or lower. After the recovery, administration can be resumed by reducing the dose by one level.
	Oculomucocutaneous syndrome (Stevens-Johnson syndrome) or toxic epidermal necrolysis (TEN)	Administration should be permanently discontinued.

* Grade should be in accordance with NCI-CTCAE v4.0.

11. ADVERSE REACTIONS
Severe skin disorders
Severe skin disorders such as toxic epidermal necrolysis (TEN),

11.1 Clinically Significant Adverse Reactions	oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme, or toxic skin eruption may occur.

7 Other antitumor agents

Regorafenib hydrate

Brand name	Stivarga tablets 40 mg (Bayer Yakuhin, Ltd.)
8. IMPORTANT PRECAUTIONS	Thrombocytopenia, neutropenia, or leukopenia may occur. Patients should be carefully monitored through periodic blood tests, etc. during treatment with this drug.
11. ADVERSE REACTIONS	Thrombocytopenia, neutropenia, leukopenia
11.1 Clinically Significant Adverse Reactions	

8 Other diagnostic agents (except extracorporeal diagnostic medicines)

Gadobutrol

Brand name	Gadovist iv injection 1.0 mol/L syringes 5 mL, 7.5 mL, 10 mL, Gadovist iv injection 1.0 mol/L 2 mL (Bayer Yakuhin, Ltd.)
11. ADVERSE REACTIONS	Shock, anaphylaxis
11.1 Clinically Significant Adverse Reactions	Shock or anaphylaxis (decreased blood pressure, dyspnoea, loss of consciousness, pharyngeal/laryngeal oedema, face oedema, respiratory arrest, cardiac arrest, etc.) may occur.
(newly added)	Acute respiratory distress syndrome, pulmonary oedema If rapidly progressive dyspnoea, hypoxaemia, or chest X-ray abnormalities such as diffuse infiltrative shadow in both lungs are observed, appropriate measures should be taken as necessary.

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 June 30, 2024)
◎: Products for which EPPV was initiated after June 1, 2024

	Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
◎	Concizumab (genetical recombination)[*1] / Alhemo Subcutaneous Injection 15 mg, 60 mg, 150 mg, 300 mg	Novo Nordisk Pharma Ltd.	June 24, 2024
◎	Fluticasone furoate/vilanterol trifenatate / Relvar 100 Ellipta 14 doses, 30 doses	GlaxoSmithKline K.K.	June 24, 2024
◎	Baricitinib[*2] / Olumiant tablets 1 mg	Eli Lilly Japan K.K.	June 17, 2024
◎	Zolbetuximab (genetical recombination) / Vyloy for I.V. infusion 100 mg	Astellas Pharma Inc.	June 12, 2024
◎	Nemolizumab (genetical recombination)[*3] / Mitchga Vials 30 mg	Maruho Co., Ltd.	June 11, 2024
◎	Susoctocog alfa (genetical recombination) / Obizur Intravenous Injection 500	Takeda Pharmaceutical Company Limited	June 10, 2024
◎	Benralizumab (genetical recombination) / Fasenra Subcutaneous Injection 10 mg Syringe	AstraZeneca K.K.	June 3, 2024
	Recombinant respiratory syncytial virus vaccine[*4] / Abrysvo intramuscular injection	Pfizer Japan Inc.	May 31, 2024
	Lebrikizumab (genetical recombination) / Ebglyss Subcutaneous Injection Syringes 250 mg, Ebglyss Subcutaneous Injection Autoinjectors 250 mg	Eli Lilly Japan K.K.	May 31, 2024
	Apadamtase alfa (genetical recombination)/ cinaxadamtase alfa (genetical recombination) / Adzynma Intravenous 1500	Takeda Pharmaceutical Company Limited	May 30, 2024
	Cysteamine hydrochloride / Cystadrops Ophthalmic Solution 0.38%	Viatris Pharmaceuticals Japan Inc.	May 30, 2024
	Lonafarnib	AnGes, Inc.	May 27,

Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
Zokinvy capsules 50 mg, 75 mg		2024
Elranatamab (genetical recombination) Elrexfio S.C. Injection 44 mg, 76 mg	Pfizer Japan Inc.	May 22, 2024
Capivasertib Truqap tablets 160 mg, 200 mg	AstraZeneca K.K.	May 22, 2024
Nirsevimab (genetical recombination) Beyfortus 50 mg solution for intramuscular injection in syringe, Beyfortus 100 mg solution for intramuscular injection in syringe	AstraZeneca K.K.	May 22, 2024
Belumosudil mesilate Rezurock Tablets 200 mg	Meiji Seika Pharma Co., Ltd.	May 22, 2024
Crovalimab (genetical recombination) Piasky for Injection 340 mg	Chugai Pharmaceutical Co., Ltd.	May 22, 2024
Sacubitril valsartan sodium hydrate[*5] Entresto Granules for Pediatric 12.5 mg, 31.25 mg	Novartis Pharma K.K.	May 22, 2024
Luspatercept (genetical recombination) Reblozyl for S.C. injection 25 mg, 75 mg	Bristol-Myers Squibb K.K.	May 20, 2024
Letermovir[*6] Prevymis Tablets 240 mg, Prevymis Intravenous Infusion 240 mg	MSD K.K.	May 17, 2024
Talazoparib tosilate Talzenna capsules 0.1 mg, 0.25 mg, 1 mg	Pfizer Japan Inc.	April 23, 2024
Evinacumab (genetical recombination) Evkeeza for Intravenous Infusion 345 mg	Ultragenyx Japan K.K.	April 17, 2024
Danicopan Voydeya tablets 50 mg	Alexion Pharma Godo Kaisha	April 17, 2024
Aflibercept (genetical recombination) Eylea 8mg solution for IVT inj. 114.3 mg/mL	Bayer Yakuhin, Ltd.	April 17, 2024
Efgartigimod alfa (genetical recombination)/ vorhyaluronidase alfa (genetical recombination) Vyvdura Combination Subcutaneous Injection	argenx Japan K.K.	April 17, 2024
Perampanel hydrate Fycompa for intravenous infusion 2 mg	Eisai Co., Ltd.	April 17, 2024
Benralizumab (genetical recombination) Fasenra Subcutaneous Injection 30 mg Syringe	AstraZeneca K.K.	March 26, 2024
Rifaximin Rifxima Tablets 200 mg	Aska Pharmaceutical Co., Ltd.	March 26, 2024

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
	Fenfluramine hydrochloride[*7] Fintepla oral solution 2.2 mg/mL	UCB Japan Co. Ltd.	March 26, 2024
	Efgartigimod alfa (genetical recombination)[*8] Vyvgart for Intravenous Infusion 400 mg	argenx Japan K.K.	March 26, 2024
	Baricitinib[*9] Olumiant tablets 2 mg, 4 mg	Eli Lilly Japan K.K.	March 26, 2024
	Adsorbed diphtheria-purified pertussis-tetanus-inactivated polio-*Haemophilus* type b conjugate combined vaccine Gobik Aqueous Suspension Syringes	The Research Foundation for Microbial Diseases of Osaka University	March 15, 2024
	Adsorbed diphtheria-purified pertussis-tetanus-inactivated polio-*Haemophilus* type b conjugate combined vaccine Quintovac Aqueous Suspension Injection	KM Biologics Co., Ltd.	March 14, 2024
	Semaglutide (genetical recombination)[*10] Wegovy Subcutaneous Injection 0.25 mg SD, 0.5 mg SD, 1.0 mg SD, 1.7 mg SD, 2.4 mg SD	Novo Nordisk Pharma Ltd.	February 22, 2024
	Tenapanor hydrochloride Phozevel Tablets 5mg, 10 mg, 20 mg, 30 mg	Kyowa Kirin Co., Ltd.	February 20, 2024
	Zilucoplan sodium Zilbrysq Syringe for S.C. Injections 16.6 mg, 23.0 mg, 32.4 mg	UCB Japan Co. Ltd.	February 16, 2024
	Concizumab (genetical recombination) Alhemo Subcutaneous Injection 15 mg, 60 mg, 150 mg, 300 mg	Novo Nordisk Pharma Ltd.	February 16, 2024
	Sacubitril valsartan sodium hydrate[*11] Entresto Tablets 50 mg, 100 mg, 200 mg	Novartis Pharma K.K.	February 9, 2024
	Empagliflozin[*12] Jardiance Tablets 10 mg	Nippon Boehringer Ingelheim Co., Ltd.	February 9, 2024
	pH4-treated acidic normal human immunoglobulin (subcutaneous injection) Cuvitru 20% S.C. Injection 2 g/10 mL, 4 g/20 mL, 8 g/40 mL	Takeda Pharmaceutical Company Limited	January 24, 2024
	Recombinant respiratory syncytial virus vaccine Arexvy Intramuscular Injection	GlaxoSmithKline K.K.	January 15, 2024
	Glucarpidase (genetical recombination) Megludase for Intravenous Use 1000	Ohara Pharmaceutical Co., Ltd.	January 4, 2024

*1 Prevention of bleeding tendency in patients with congenital haemophilia who don't have inhibitors against blood coagulation factor VIII or IX.

*2 Polyarticular-course juvenile idiopathic arthritis in patients who have not responded sufficiently to conventional

treatments

*3 Addition of a pediatric dosage indicated for the following diseases in patients who have not responded sufficiently to conventional treatments.
Pruritus associated with atopic dermatitis
Prurigo nodularis

*4 Prevention of infections caused by RS virus in individuals aged 60 years and older

*5 Addition of a pediatric dosage indicated for chronic heart failure

*6 Prophylaxis of cytomegalovirus infections in organ transplant recipients

*7 Concomitant therapy with antiepileptic drugs for epileptic seizures in patients with Lennox-Gastaut syndrome who are not sufficiently responsive to other antiepileptic drugs

*8 Chronic idiopathic thrombocytopenic purpura

*9 Polyarticular-course juvenile idiopathic arthritis in patients who have not responded sufficiently to conventional treatments

*10 Treatment of obesity
The use is limited to patients with either hypertension, dyslipidaemia, or type 2 diabetes mellitus who have not adequately responded to treatment with diet and exercise therapy and meet the following conditions:
•BMI of 27 kg/m^2 or greater in the presence of at least two obesity-related comorbidities
•BMI of 35 kg/m^2 or greater

*11 Addition of a pediatric dosage indicated for chronic heart failure

*12 Chronic kidney disease