Pharmaceuticals and Medical Devices Safety Information

No. 422 August 2025

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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

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This service is available only in Japanese.

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Pharmaceuticals and Medical Devices Safety Information

No. 422 August 2025

Ministry of Health, Labour and Welfare
Pharmaceutical Safety 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 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
ANCA	Anti-Neutrophil Cytoplasmic Antibody
APTT	Activated partial thromboplastin time
ASO	Anti-Streptolysin-O
BMI	Body Mass Index
CA125	Cancer Antigen 125
CEA	Carcinoembryonic Antigen
CMV	Cytomegalovirus
COVID	Coronavirus disease
CR	Complete Response
CT	Computed Tomography
DLST	Drug-induced Lymphocyte Stimulation Test
ECOG	Eastern Cooperative Oncology Group
EPPV	Early Post-marketing Phase Vigilance
EGFR	Epidermal Growth Factor Receptor
FDG	Fluorodeoxyglucose
FY	Fiscal Year
HCV/RNA	Hepatitis C Virus-Ribonucleic Acid
HER2	Human Epidermal Growth Factor Receptor 2
HPF	High Power Field
IFN-γ	Interferon gamma
IgG	Immunoglobulin G
IL-6	Interleukin-6
irAE	Immune-related Adverse Events
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
MPO-ANCA	Myeloperoxidase-anti-neutrophil Cytoplasmic Antibodies
NT-proBNP	N-terminal pro-Brain Natriuretic Peptide
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PD-L1	Programmed Death-ligand 1
PIP/MIM	Pharmaceutical Industry Promotion and Medical Information Management
PMDA	Pharmaceuticals and Medical Devices Agency
PR	Partial Response
PR-3-ANCA	Proteinase 3-ANCA
PSB	Pharmaceutical Safety Bureau
PT	Preferred Terms
PT-INR	Prothrombin Time-International Normalized Ratio
RMP	Risk Management Plan
RPR	Rapid Plasma Reagin
SMQ	Standardised MedDRA Queries
TPLA	Treponema Pallidum Latex Agglutination
VAB	Vacuum Assisted Biopsy
WF	Whole Field
β2-MG	β2-microglobulin

1

Utilization of Risk Management Plan (RMP)

1. Introduction

In order to ensure the safety of drugs, it is important to always consider measures to properly manage risks from the development stage to the post-marketing stage. The Risk Management Plan (RMP) summarizes consistent risk management from drug development to post-marketing stages in one document in an easy-to-understand manner, to ensure implementation of the evaluations according to the progress of surveys/studies and activities to reduce risks either as needed or on a regular basis. In addition, it is expected that disclosing an RMP and widely sharing the contents of post-marketing risk management with healthcare professionals will lead to further enhancement and strengthening of post-marketing safety measures.

This document is intended to explain what an RMP is and to introduce recent developments related to an RMP. Please read this document and use RMP materials more effectively in clinical practice.

2. What is an RMP

An RMP is a document that summarizes (1) important adverse reactions that are clearly related or suspected to be related to drugs and missing information (safety specifications), (2) post-marketing information collection activities (pharmacovigilance activities), and (3) efforts to reduce risks of drugs such as provision of information to healthcare professionals and setting of conditions for use (risk minimization activities) for individual drugs.

Activities to reduce/avoid risks, such as examining how to provide information on risks and missing information described in the RMP, are referred to as risk minimization activities. Risk minimization activities are divided into the activities performed for all drugs (routine risk minimization activities) and those performed based on the characteristics of drugs (additional risk minimization activities). Providing information through package inserts and drug guides for patients is included in routine risk minimization activities. On the other hand, setting conditions for use and providing information through materials, etc. are examples of additional risk minimization activities. RMP materials include materials for patients that explain subjective symptoms of adverse reactions in plain language, and materials for healthcare professionals that summarize information necessary for the proper use of drugs.

The contents of these RMP materials were checked by the PMDA during the preparation process and are indicated by the “RMP mark” to distinguish them from other materials prepared by marketing authorization holders. Healthcare professionals are encouraged to identify RMP materials by locating the “RMP mark” and to proactively utilize these materials.

Also, please refer to materials that explain RMP in an easy-to-understand manner on the PMDA website.

- ✓ “Learn about RMP in 3 Minutes” (only in Japanese)
  This is an A4-size double-sided document that explains RMP.
- ✓ “Simple Enough to Start! How to use RMP” (only in Japanese)
  This is e-learning content in which a hospital pharmacist explains RMP and the materials prepared and provided for additional risk minimization activities through videos. The contents consist of two topics: “What’s RMP?” and “Let's Try RMP!” and anyone can view them free of charge.

PMDA website: Risk Management Plan (in Japanese)

https://www.pmda.go.jp/english/safety/info-services/drugs/rmp/0001.html (in English)

3. Medication instructions and pharmaceutical management based on RMP

At the Central Social Insurance Medical Council for the revision of medical service fees in FY 2024, the following data were presented:

- In pharmacies, materials based on the RMP for patients have been used for explanations to patients in situations where more thorough medication instructions are required.
- Utilization of information materials for patients based on the RMP in medication instruction has led to patients’ behavior of securing safety.

In the revision of medical service fees in FY 2024 (dispensing fee), analysis and evaluation using the RMP were added to the requirements for calculation of the dispensing management fee, and an additional fee for providing instructions using RMP materials for patients (additional fee for specified medication instruction 3 a) was established.

Utilizing RMP information to analyze the content of prescriptions and provide instructions and management in medical practice is expected to lead to higher-quality pharmaceutical management and instruction and post-marketing safety measures.

4 Review of the RMP system in association with the revision of the Pharmaceuticals and Medical Devices Act in 2025

Since products with limited safety information at the time of approval and drugs manufactured using new technologies have been increasing, it is important to reform the system to focus on collecting information in a planned manner based on the RMP to consider the safety measures instead of widely collecting and reporting adverse reactions, etc. and to establish a system for more effective implementation of risk-based safety measures.

Under the current Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as “the Pharmaceuticals and Medical Devices Act”), the preparation of an RMP is specified as a condition for marketing approval of drugs, etc. This condition can be lifted when the contents of activities based on the plan were confirmed at the time of re-examination of the approval. However, there is an inconvenience that safety measures based on RMP will be uniformly completed after the condition for approval has been lifted.

Therefore, in the revision of Pharmaceuticals and Medical Devices Act in 2025, it was decided that preparation, reporting, and implementation of the RMP when necessary, including in the case where it is required in post-marketing settings, would be specified as an obligation in the Pharmaceuticals and Medical Devices Act, rather than specifying implementation of risk management based on the RMP as a condition for approval, so that prompt action can be taken according to the characteristics of drugs or risks when any safety concern occurs.

This revision is supposed to be enforced within 2 years after the promulgation of the revised

Pharmaceuticals and Medical Devices Act (May 21, 2025), and detailed examination of the system is currently underway toward the enforcement.

5. Conclusion

Drugs can be used more effectively and safely through the accumulation of post-marketing experience after approval, which is granted based on limited data, including clinical study results. It is extremely important for healthcare professionals, by utilizing the RMP in medical practice, to understand what important safety concerns (safety specifications) and efficacy specifications exist at this point in time, on what grounds they have been established, and what kinds of activities, and for what purposes, are planned and implemented for them. This is essential to promote the proper use of drugs and ensure patient safety.

In addition to RMP and RMP materials, various tools, such as drug guides for patients, are available on the PMDA website (only in Japanese). We encourage you to use these tools and cooperate further in safety measures for drugs.

6. Reference

• Risk Management Plan (RMP)
https://www.pmda.go.jp/safety/info-services/drugs/items-information/rmp/0002.html (in Japanese)
https://www.pmda.go.jp/english/safety/info-services/drugs/rmp/0001.html (in English)
• General Assembly of the Central Social Insurance Medical Council on November 29, 2023 (the 568th assembly) So-2
https://www.mhlw.go.jp/content/12404000/001172376.pdf (only in Japanese)
• Summary of Revision of Medical Service Fees (Dispensing) in 2024
https://www.mhlw.go.jp/content/12400000/001238903.pdf (only in Japanese)
• Summary on System Reform of Pharmaceuticals and Medical Devices Act, etc. (January 10, 2025, the Subcommittee for Pharmaceuticals and Medical Devices Regulation of the Health Science Council of MHLW)
https://www.mhlw.go.jp/content/11120000/001371285.pdf (only in Japanese)
• Promulgation of the Act Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PSB Notification No. 0521-1 and PIP/MIM Notification No. 0521-4 dated May 21, 2025)
https://www.mhlw.go.jp/content/11120000/001491554.pdf (only in Japanese)
(2.I.1.(9) Matters related to preparation, etc. of plans for collection, etc. of information on the safety and efficacy of drugs)

2

Important Safety Information

Regarding the revision of the PRECAUTIONS of package inserts of drugs in accordance with the Notification dated July 30 , 2025, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 Semaglutide (genetical recombination)

Brand name (name of company)	Ozempic Subcutaneous Injection 2 mg (Novo Nordisk Pharma Ltd.)
Therapeutic category	Other hormone preparations (including antihormone preparations), antidiabetic agents
Indications	•Wegovy Subcutaneous Injection Obesity For use only in patients with any of hypertension, hyperlipidemia or type 2 diabetes mellitus who have not responded sufficiently to diet therapy and exercise therapy, and who meet the following conditions: ·BMI of 27 kg/m2 or greater in the presence of at least two obesity-related comorbidities ·BMI of 35 kg/m2 or greater •Ozempic Subcutaneous Injection, Rybelsus tablets Type 2 diabetes mellitus

PRECAUTIONS (Revised language is underlined.)

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc.** **(newly added)**	Patients with a medical history of abdominal surgery or ileus Ileus, including intestinal obstruction, may occur.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Ileus Ileus, including intestinal obstruction, may occur. If any abnormalities such as severe constipation, abdominal distension, persistent abdominal pain, or vomiting are observed, administration of this drug should be discontinued, and appropriate measures should be taken.
Reference information	Number of cases (for which a causal relationship between the drug and the event is reasonably possible) that fell under SMQ “gastrointestinal obstruction,” those falling under the PTs of “impaired gastric emptying,” “oesophageal obstruction,” “necrotising oesophagitis,” or “gastric volvulus,” excluding those whose site of onset of the adverse event is not intestinal, among those collected in the PMDA's safety database for drugs Cases involving ileus reported in Japan:

7 (including 1 case in which the drug was administered outside the approved indications) (No patient mortalities)
Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 112,000
Japanese market launch: May 2022

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Male 50s	Type 2 diabetes mellitus (hypertension, hepatic steatosis, gallstones)	0.5 mg once a week ↓ 1.0 mg once a week ↓ Discontinuation ↓ 0.5 mg once a week	**Ileus**	
				Before start of administration	Previous treatment drugs: Dulaglutide (genetical recombination), metformin, dapagliflozin propylene glycolate hydrate
				Day 1 of administration	Administration of semaglutide (genetical recombination) 0.5 mg/week was initiated. Administration of metformin and dapagliflozin propylene glycolate hydrate was continued.
				Day 14 of administration	The dose of semaglutide (genetical recombination) was increased to 1.0 mg/week. Abdominal pain and queasy began to appear after use.
				Day 42 of administration	Abdominal distension was present. The patient had bowel movements, but he complained of constipation at the time of the outpatient visit.
				Day 98 of administration	The patient complained of constipation and abdominal distension at the time of the outpatient visit.
				Day 119 of administration (day of discontinuation)	Aggravation of abdominal distension and vomiting were present. The patient visited the surgery department and was admitted to the hospital with a diagnosis of ileus. A CT scan revealed a niveau in the small intestine (+), gas in the colon, and intraperitoneal free air (-). Volvulus of the bowel was not observed on a CT scan. Administration of semaglutide (genetical recombination) was discontinued. The symptoms improved with fasting and gastric tube insertion.
				4 days after discontinuation	The patient started eating.
				6 days after discontinuation	Ileus resolved, and the patient was discharged from the hospital.
				35 days after discontinuation	Administration of semaglutide (genetical recombination) 0.5 mg/week was restarted.
	Concomitant drugs: Metformin, dapagliflozin propylene glycolate hydrate, nifedipine CR, telmisartan				

2 Tirzepatide

Brand name (name of company)	Mounjaro Subcutaneous Injection 2.5 mg Ateos, 5 mg Ateos, 7.5 mg Ateos, 10 mg Ateos, 12.5 mg Ateos, 15 mg Ateos (Eli Lilly Japan K.K.)
Therapeutic category	Other hormone preparations (including antihormone preparations), antidiabetic agents
Indications	•Zepbound Subcutaneous Injection Obesity For use only in patients with any of hypertension, hyperlipidemia or type 2 diabetes mellitus who have not responded sufficiently to diet therapy and exercise therapy, and who meet the following conditions: ·BMI of 27 kg/m2 or greater in the presence of at least two obesity-related comorbidities ·BMI of 35 kg/m2 or greater •Mounjaro Subcutaneous Injection Type 2 diabetes mellitus

PRECAUTIONS (Revised language is underlined.)

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc.** **(newly added)**	Patients with a medical history of abdominal surgery or ileus Ileus, including intestinal obstruction, may occur.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Ileus Ileus, including intestinal obstruction, may occur. If any abnormalities such as severe constipation, abdominal distension, persistent abdominal pain, or vomiting are observed, administration of this drug should be discontinued, and appropriate measures should be taken.
Reference information	Number of cases (for which a causal relationship between the drug and the event is reasonably possible) that fell under SMQ “gastrointestinal obstruction,” those falling under the PTs of “impaired gastric emptying,” “oesophageal obstruction,” “necrotising oesophagitis,” or “gastric volvulus,” excluding those whose site of onset of the adverse event is not intestinal, among those collected in the PMDA's safety database for drugs Cases involving ileus reported in Japan: 2 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 581,900 Japanese market launch: [1] Subcutaneous Injection 2.5 mg Ateos, 5 mg Ateos:April 2023 [2] Subcutaneous Injection 7.5 mg Ateos, 10 mg Ateos,12.5 mg Ateos, 15 mg Ateos:June 2023

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Female 70s	Type 2 diabetes mellitus (hypertension, lipid metabolism disorder, hyperuricaemia)	2.5 mg once a week ↓ Discontinuation	**Intestinal obstruction (paralytic)**	
				Day 1 of administration	Administration of tirzepatide was initiated after switching from dulaglutide.
				Day 266 of administration	No particular abnormality was present. No pyrexia was present.
				Around Day 284 of administration	Abdominal distension was observed.
				Day 291 of administration	The patient visited the hospital for abdominal distension. An abdominal X-ray showed marked small intestinal gas. Flatus was noted, and no tenderness was present. Vital signs were normal. Administration of tirzepatide was continued. No pyrexia was present.
				Day 293 of administration	Since the small intestinal gas decreased, the patient was advised to undergo endoscopy in consideration of tumorous changes in the large intestine, etc., but she refused the procedure. An abdominal and pelvic CT scan showed small intestinal gas. No other abnormalities that could cause intestinal obstruction or tumorous changes in the large intestine were noted. This event was diagnosed as paralytic intestinal obstruction. Administration of a macrogol/sodium chloride/sodium bicarbonate/potassium chloride combination drug 13.704 g/day was initiated for treatment.
				Day 297 of administration	The patient was admitted to another hospital for aggravation of abdominal symptoms. She did not undergo endoscopy even during hospitalization. A CT scan was performed under fasting conditions, and her clinical course was observed.
				Day 305 of administration (day of discontinuation)	Intestinal obstruction (paralytic) resolved. Administration of tirzepatide was discontinued. The patient was subsequently discharged from the hospital.
				6 days after discontinuation	There was no pyrexia, no significant change in blood pressure, or no marked change in heart rate.

Laboratory test value

Test item (unit)	Day 266 of administration	Day 291 of administration	6 days after discontinuation
Blood pressure (mmHg)	130/80	130/80	-
Heart rate (beats/min)	78	78	-
Red blood cell count ($\times 10^4/mm^3$)	392	435	358
Haemoglobin (g/dL)	12.7	13.3	11.6
Haematocrit (%)	35.8	41.1	32.8
Platelet count ($\times 10^4/mm^3$)	26.9	32.1	26.4
White blood cell count ($/mm^3$)	10,900	11,100	7,700
Ca19-9	-	38.3	-
CEA	-	3.4	-

Concomitant drugs: Valsartan, pitavastatin calcium, febuxostat, amlodipine besilate, famotidine, adenosine triphosphate disodium hydrate, betahistine mesilate, shakuyakukanzoto

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
2	Male 50s	Type 2 diabetes mellitus (no complication)	2.5 mg once a week ↓ Discontinuation	**Paralytic ileus**	
				Day of administration	Administration of tirzepatide was initiated.
				Day 1 of administration	The patient started to have a churning of the stomach. He vomited. Right flank pain was gradually aggravated.
				Around Day 2 of administration (day of discontinuation)	The patient was transported by ambulance and admitted to the hospital. At the time of transportation, abdominal distension was prominent. An abdominal X-ray showed expansion of small intestinal gas. Niveau formation was observed. CT and abdominal X-ray findings: Ileus. He was diagnosed with paralytic ileus. A nasogastric tube was inserted, and administration of cefmetazole 1 g twice a day was initiated. Administration of tirzepatide, luseogliflozin hydrate, and metformin hydrochloride was discontinued, and only sitagliptin phosphate hydrate was continued. Blood sugar and blood pressure remained between 110 and 180 mg/dL and around 120/80 mmHg, respectively.
				1 day after discontinuation	The patient felt better the day after admission.
				2 days after discontinuation	The tube was replaced with an ileus tube, and drainage was continued.
				9 days after discontinuation	Resolution of ileus was confirmed, and an ileus tube was removed.
				11 days after discontinuation	The patient started eating (low-residue diet: 1,400 Kcal).
				Date unknown	Administration of daikenchuto and mosapride citrate hydrate was initiated for bowel movement control.
				13 days after discontinuation	Paralytic ileus resolved.
				16 days after discontinuation	The symptoms did not relapse, and the patient was discharged from the hospital. Daikenchuto and mosapride citrate hydrate were continuously administered. After the discharge from the hospital, luseogliflozin hydrate, metformin hydrochloride, and sitagliptin phosphate hydrate were prescribed for the treatment of diabetes mellitus.
	Concomitant drugs: Luseogliflozin hydrate, metformin hydrochloride, candesartan cilexetil, sacubitril valsartan sodium hydrate				

3 Afatinib maleate

Brand name (name of company)	Giotrif Tablets 20 mg, 30 mg, 40 mg (Nippon Boehringer Ingelheim Co ., Ltd.)
Therapeutic category	Other antitumor agents
Indications	Unresectable or recurrent *EGFR* mutation-positive non-small-cell lung cancer

PRECAUTIONS (Revised language is underlined.)

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Anaphylaxis
Reference information	Number of cases (for which a causal relationship between the drug and the event is reasonably possible) collected in the PMDA's safety database for drugs Cases involving anaphylaxis 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 1,650 Japanese market launch: May 2014

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Female 50s	Non-small cell lung cancer (none)	30 mg for 3 days	**Anaphylactic shock**	
				6 days before administration	The patient started receiving whole brain irradiation for brain metastases of lung cancer. Concentrated glycerin for injection 200 mg and dexamethasone 3.3 mg were initiated for prevention of brain oedema.
				Day 1 of administration	The patient was admitted to the hospital for the introduction of afatinib maleate as the treatment of lung cancer (7th line) and started receiving it. Administration of hangeshashinto 7.5 g was initiated for prevention of diarrhoea.
				Day 2 of administration	Wheals appeared on the face, upper extremities, etc. The skin eruption disappeared approximately 1 hour after administration of 1 tablet of chlorpheniramine 2 mg.
				Day 3 of administration (day of discontinuation)	Two tablets of chlorpheniramine 2 mg divided into 2 doses were administered. Around 3 hours after administration of afatinib maleate, redness and wheals appeared around the face and nose, on the thighs, and on the abdomen, which were aggravated to generalized erythema in several minutes. SpO_2 was 95% (no dyspnoea), body temperature was 36.8 degrees C, and systolic blood pressure decreased to the 50-69 mmHg range. Intramuscular injection of adrenaline 0.3 mg, and drip infusion of hydrocortisone 200 mg, famotidine 20 mg, and chlorpheniramine 5 mg were administered. Approximately 1 and a half hours after the onset of the symptoms, blood pressure recovered to the 100 mmHg range. The rash/skin eruption tended to disappear. Administration of afatinib maleate, hangeshashinto, and chlorpheniramine tablets was discontinued.
				2 days after discontinuation	Drip infusion of chlorpheniramine injection, famotidine injection, and hydrocortisone injection was terminated. The skin eruption was improving to the extent that it was seen only around the lips.
	Suspected concomitant drugs: Hangeshashinto Concomitant drugs: Concentrated glycerin, fructose, dexamethasone sodium phosphate, chlorpheniramine hydrochloride, esomeprazole magnesium hydrate, rebamipide, dextromethorphan hydrobromide hydrate, mecobalamin, diquafosol sodium, loxoprofen sodium hydrate, levofloxacin hydrate, heparinoid				

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
Administration duration</th><th colspan="2">Adverse reaction</th></tr>
<tr><th>Sex/
age</th><th>Reason for use
(complication)</th><th colspan="2">Clinical course and treatment</th></tr>
<tr><td>2</td><td>Male
40s</td><td>Lung adenocarcinoma
(none)</td><td>40 mg
for 7 days
↓
30 mg
for 6 days
↓
Discontinuation
↓
20 mg
for 4 days
↓
Discontinuation
↓
20 mg
for 1 day
↓
Discontinuation</td><td colspan="2">Allergy</td></tr>
<tr><td colspan="3" rowspan="7"></td><td rowspan="7"></td><td>6 years before start of administration</td><td>Administration of afatinib maleate 40 mg was initiated.
The dose was decreased to 30 mg due to skin eruption on the 7th day of administration.
Administration was discontinued due to enanthema on the 13th day of administration.
It improved after a short-term use of prednisolone 30 mg.</td></tr>
<tr><td>Day 1 of administration</td><td>Since the previous discontinuation was not due to PD (progressive disease), administration of afatinib maleate 20 mg was initiated.</td></tr>
<tr><td>Day 2 of administration</td><td>The patient visited the hospital for pyrexia and queasy. Since his family member in the same household had pyrexia, he was determined to have an infection and received metoclopramide and famotidine.</td></tr>
<tr><td>Day 4 of administration (day of discontinuation)</td><td>The patient was urgently admitted to the hospital for pyrexia, severe queasy, vomiting, and diarrhoea. Administration of afatinib maleate was discontinued. His clinical course was observed with fluid replacement and administration of a general antibiotic (sulbactam/ampicillin), and the symptoms gradually improved.</td></tr>
<tr><td>9 days after discontinuation (day 1 of readministration, day of discontinuation of readministration)</td><td>Since the symptoms improved, afatinib maleate 20 mg was administered in an inpatient setting. Remarkable queasy, vomiting, and diarrhoea relapsed approximately 30 minutes after administration. Pyrexia and increased creatinine levels also occurred, and the patient was determined to have allergies. Chlorpheniramine maleate, water-soluble prednisolone 50 mg, acetaminophen, and metoclopramide were administered.</td></tr>
<tr><td>1 day after discontinuation of readministration</td><td>The symptoms improved.</td></tr>
<tr><td colspan="5">Laboratory test value
<table>
<tr><th>Test item (unit)</th><th>Day 2 of administration</th><th>Day 4 of administration (day of discontinuation)</th><th>1 day after discontinuation</th><th>Day 1 of readministration</th><th>1 day after discontinuation of readministration</th><th>3 days after discontinuation of readministration</th><th>44 days after discontinuation of readministration</th></tr>
<tr><td>Creatinine (mg/dL)</td><td>1.64</td><td>3.49</td><td>2.45</td><td>1.67</td><td>3.64</td><td>1.67</td><td>-</td></tr>
<tr><td>C-reactive protein (mg/dL)</td><td>0.98</td><td>8.80</td><td>13.42</td><td>1.14</td><td>7.29</td><td>0.52</td><td>-</td></tr>
<tr><td>DLST</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>Positive</td></tr>
</table></td></tr>
<tr><td colspan="5">Concomitant drugs: Metoclopramide, famotidine</td></tr>
</table>

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
3	Female 50s	Right middle lobe lung cancer (multiple brain metastases, bronchial asthma)	40 mg for 1 day	**Anaphylaxis**	
				Day 1 of administration (day of discontinuation)	Administration of afatinib maleate was initiated. Two hours and 15 minutes after administration, abdominal pain developed. Two hours and 30 minutes after administration, a map-like skin eruption developed on the forearms, and skin eruption developed on the face. Dyspnoea ($SatO_2$ 97%→92%), palpitations (+), decreased blood pressure (136/78 mmHg before administration → 104/58 mmHg after administration), conjunctival swelling (+), hyperaemia (+), oral redness (+), increased pulse rate (78 bpm before administration → 102 bpm after administration). The patient started receiving 2 L of oxygen and received betamethasone sodium phosphate 4 mg (1A). D-chlorpheniramine maleate (1A) and famotidine (1A) were administered by drip infusion. Two hours and 40 minutes after administration, blood pressure was 111/75 mmHg, and pulse rate was 104 bpm. Two hours and 50 minutes after administration, she had symptoms of diarrhoea. The skin eruption slightly abated after excretion. A bifidobacterial preparation was administered. Three hours and 40 minutes after administration, $SatO_2$ was 93%-94% (under 2 L of oxygen). The skin eruption on the face and erythema on the upper extremities disappeared. Blood pressure was 126/84 mmHg. Seven hours after administration, blood pressure was 130/84 mmHg, and pulse rate was 82 bpm. She was off oxygen after confirmation of $SatO_2$ of 97% (room air). Administration of afatinib maleate was discontinued. Anaphylaxis and diarrhoea resolved.
				1 day after discontinuation	Blood pressure was 126/80 mmHg.
	Concomitant drugs: None				

4 Fulvestrant

Brand name (name of company)	Faslodex Intramuscular Injection 250 mg (AstraZeneca K.K.)
Therapeutic category	Other antitumor agents
Indications	Breast cancer

PRECAUTIONS (Revised language is underlined.)

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Anaphylaxis
Reference information	Number of cases (for which a causal relationship between the drug and the event is reasonably possible) collected in the PMDA's safety database for drugs Cases involving anaphylaxis reported in Japan:6(No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 15,600 Japanese market launch: November 2011

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Female 70s	Female breast cancer (hypertension, osteoporosis, osteoarthritis, constipation, depression)	500 mg once every 4 weeks 1,178 days ↓ Discontinuation	**Decreased blood pressure, anaphylactic shock** Past history, allergy history, and adverse drug reaction history: None Family history: Unknown	
				14 years and 4 months before administration	The patient was diagnosed with female breast cancer. She underwent a right mastectomy.
				7 years before administration	The patient underwent chest wall lymph node metastasis resection.
				13 days before administration	The patient received 60 Gy of radiotherapy to the right parasternal lymph nodes. (until 12 days after administration of fulvestrant).
				Day 1 of administration	Administration of fulvestrant was initiated.
				3 years and 3 months after administration (day of discontinuation)	
				47 minutes before administration	BP was 111/82 mmHg, and pulse rate was 75 (beats/min). The patient showed no change in her physical condition, and there were no noteworthy findings at the time of medical examination.
				At the time of administration	With the patient in a prone position, fulvestrant (2 syringes) was administered in the bilateral buttocks. During the administration, she said that she was "going to cough," and mild cough was observed. After the completion of administration, she stood up and began to complain of feeling mildly poorly while wearing shoes. Although she took a sitting position on the bed, she kept her eyes closed. She responded, but her consciousness was slightly hazy. The patient gradually became unable to maintain an upright posture and tilted backward. Therefore, bed rest and leg elevation were performed. Her vital signs immediately after that showed BP of 72/45 mmHg, pulse rate of 62 (beats/minute), and SpO_2 of 95%. Anaphylactic shock, decreased blood pressure, staggering, and facial pallor were observed. No mucocutaneous symptoms were observed. After bed rest, her consciousness rapidly became clear. Intravenous drip infusion of physiological saline 500 mL was initiated.
				10 minutes after administration	BP was 81/44 mmHg.
				23 minutes after administration	BP was 97/55 mmHg, and pulse rate was 65 (beats/min). Intravenous drip infusion of Sol-Melcort 125 mg and physiological saline 500 mL was initiated.
				Unknown	BP was 115/70 mmHg, and feeling poorly disappeared.

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
				1 hour and 45 minutes after administration	Anaphylactic shock, decreased blood pressure, staggering, feeling poorly and cough resolved.
				2 hours and 35 minutes after administration	After the course observation in the hospital, the patient went home.
				Fulvestrant was not readministered.	

Laboratory test value

Test item (unit)	3 years and 2 months after administration	3 years and 3 months after administration (day of discontinuation)				
		47 minutes before administration	At the time of administration	10 minutes after administration	23 minutes after administration	Unknown
Pulse rate (beats/min)	86	75	62	-	65	-
Systolic blood pressure (mmHg)	126	111	72	81	97	115
Diastolic blood pressure (mmHg)	86	82	45	44	55	70
SpO2 (%)	-	-	95	-	-	-

Concomitant drugs: Denosumab (genetical recombination), amlodipine besilate, magnesium oxide, etizolam, eldecalcitol

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
2	Female 50s	Female breast cancer (none)	500 mg once every 4 weeks ongoing	**Anaphylaxis** Past history, allergy history, adverse drug reaction history, family history, concomitant drugs: None	
				3 years and 3 months before administration	The patient made the first visit to the hospital for right breast cancer (T3, N+, M0). VAB: 1DC, NG2, ER/PgR/HER2: 8/0/0, Ki67: 77%.
				3 years and 2 months before administration	The patient received 4 cycles of EC as preoperative chemotherapy (for 2 months).
				3 years before administration	Paclitaxel was administered as preoperative chemotherapy (weekly) (for 10 weeks).
				2 years and 8 months before administration	The patient underwent a right mastectomy and axillary clearance. The pathological findings were scirrhous carcinoma. ypT: 9.8 cm, NG1, S+, ly1, V0, ypN+
				2 years and 7 months before administration	Radiotherapy was initiated. The patient received irradiation to the right chest wall with 50 Gy/25 Fr.
				1 month before administration	Recurrence in the right chest wall and left axillary lymph nodes was noted.
				Day 1 of administration	Administration of fulvestrant was initiated.
				Date unknown	The response rate was PR to SD.
				2 years after administration	At the time of administration of fulvestrant, consecutive sneezing, flushed face, and redness from the upper extremities to the precordial region were observed, and allergic rhinitis and allergic dermatitis developed. No dyspnoea was present. Itching improved within 15 minutes. All symptoms resolved within 20 minutes after the onset, and the patient went home without any problem. There was no problem with fulvestrant thereafter.
				2 years and 8 months after administration	
				Approximately 1 minute after administration	Approximately 1 minute after administration of fulvestrant, anaphylaxis developed with queasy, abdominal pain, dyspnoea, mild pharyngeal wheezing, flushed face, palpebral conjunctival hyperaemia, and extensive erythema on the lower body. HR: 110, BP: 87/53 mmHg, SpO_2: 99%, RR: 16.
				4 minutes after administration	Adrenaline 0.3 mg was intramuscularly injected.
				15 minutes after administration	HR: 108, BP: 83/53 mmHg, SpO_2: 99%, RR: 12.
				30 minutes after administration	The symptoms almost completely disappeared. HR: 68, BP: 109/56 mmHg, SpO_2: 99%, RR: 12.
				40 minutes after administration	Anaphylaxis resolved.
				42 minutes after administration	The patient went home with a prescription of Polaramine 2 mg 1 tablet 3 times a day.
				Date unknown	Despite readministration of fulvestrant, no recurrence was noted.

<table>
<tr><td rowspan="2">No.</td><td colspan="2">Patient</td><td rowspan="2">Daily dose/
Administration duration</td><td colspan="2">Adverse reaction</td></tr>
<tr><td>Sex/
age</td><td>Reason for use
(complication)</td><td colspan="2">Clinical course and treatment</td></tr>
<tr><td></td><td></td><td></td><td></td><td colspan="2">Administration of fulvestrant was ongoing.</td></tr>
<tr><td></td><td colspan="5">Laboratory test value
<table>
<tr><th rowspan="2">Test item (unit)</th><th colspan="3">2 years and 8 months after administration</th></tr>
<tr><th>Approximately 1 minute after administration</th><th>15 minutes after administration</th><th>30 minutes after administration</th></tr>
<tr><td>Heart rate (HR) (bpm)</td><td>110</td><td>108</td><td>68</td></tr>
<tr><td>Blood pressure [systolic/diastolic] (BP) (mmHg)</td><td>87/53</td><td>83/53</td><td>109/56</td></tr>
<tr><td>Respiratory rate (RR) (breaths/min)</td><td>16</td><td>12</td><td>12</td></tr>
<tr><td>SpO_2 (%)</td><td>99</td><td>99</td><td>99</td></tr>
</table>
Concomitant drugs: None</td></tr>
</table>

5 Sunitinib malate

Brand name (name of company)	Sutent Capsule 12.5 mg (Pfizer Japan Inc.) and the others
Therapeutic category	Other antitumor agents
Indications	·Imatinib-resistant gastrointestinal stromal tumour ·Radically unresectable or metastatic renal cell carcinoma ·Pancreatic neuroendocrine tumour

PRECAUTIONS (Revised language is underlined.)

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Hyperammonaemia Hyperammonaemia may occur even in the absence of abnormal hepatic function. If disturbed consciousness is observed, measurement of blood ammonia levels should be considered.
Reference information	Number of cases (for which a causal relationship between the drug and the event is reasonably possible) collected in the PMDA's safety database for drugs Cases involving hyperammonaemia reported in Japan: 1 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 1,563 Japanese market launch: June 2008

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Male 70s	Gastrointestinal stromal tumour, pancreatic neuroendocrine tumour	37.5 mg for 8 days ↓ Discontinuation ↓ 25 mg for 5 days ↓ Discontinuation ↓ 25 mg for 1 day ↓ Discontinuation	**Hyperammonaemia** Past history: Chronic hepatitis C Height: 170-179 cm range, Weight: 50-59 kg range	
				Day 1 of administration	Administration of sunitinib malate 37.5 mg once daily was initiated for gastrointestinal stromal tumour and pancreatic neuroendocrine tumour.
				Day 6 of administration	Inconsistent speech and behavior were noted. Hyperammonaemia developed.
				Day 8 of administration (day of discontinuation)	Disturbed consciousness was observed, and administration of sunitinib malate was discontinued. Administration of an amino acid preparation for hepatic failure was initiated. Although the patient had a history of hepatitis, no HCV/RNA was detected, and reactivation was ruled out.
				7 days after discontinuation (Day 1 of readministration)	Since disturbed consciousness improved, administration of an amino acid preparation for hepatic failure was discontinued. The dose of sunitinib malate was reduced to 25 mg, and once-daily administration was resumed.
				Day 5 of readministration (day of discontinuation of readministration)	Administration of sunitinib malate was discontinued. Administration of an elemental diet for hepatic failure was initiated.
				11 days after discontinuation of readministration	Administration of the elemental diet for hepatic failure was discontinued.
				21 days after discontinuation of readministration (Day 1 of re-readministration)	Administration of sunitinib malate 25 mg once every other day was resumed.
				Day 2 of re-readministration (day of discontinuation of re-readministration)	Disturbed consciousness was observed, and administration of sunitinib malate was discontinued. Administration of an amino acid preparation for hepatic failure was resumed.
				5 days after discontinuation of re-readministration	A CT scan was performed, showing no findings that could cause hepatic function disorder.
				9 days after discontinuation of re-readministration	Administration of an amino acid preparation for hepatic failure was terminated.
				12 days after discontinuation of re-readministration	Disorientation was observed, and administration of an amino acid preparation for hepatic failure was resumed.
				16 days after discontinuation of re-readministration	Disturbed consciousness improved.
				31 days after discontinuation of re-readministration	Administration of regorafenib hydrate was initiated.
				36 days after discontinuation of re-readministration	On Day 6 of regorafenib hydrate administration, disturbed consciousness was noted.

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
					(blood ammonia 173 μg/dL, AST 22 IU/L, ALT 13 IU/L) Administration of regorafenib hydrate was discontinued. Administration of an amino acid preparation for hepatic failure was resumed.
				42 days after discontinuation of re-readministration	Disturbed consciousness improved 6 days after discontinuation of regorafenib hydrate. Electroencephalography showed no findings such as epilepsy. Administration of an amino acid preparation for hepatic failure was terminated. Administration of L-arginine L-glutamate hydrate was started.
				45 days after discontinuation of re-readministration	Administration of L-arginine L-glutamate hydrate was discontinued 9 days after discontinuation of regorafenib hydrate. (blood ammonia 23 μg/dL, AST 24 IU/L, ALT 12 IU/L)
				55 days after discontinuation of re-readministration	No disturbed consciousness was observed 19 days after discontinuation of regorafenib hydrate. (AST 19 IU/L, ALT 8 IU/L)
				66 days after discontinuation of re-readministration	Hyperammonaemia resolved 30 days after discontinuation of regorafenib hydrate. There was no relapse of hepatic function disorder, and the patient was discharged from the hospital.

Laboratory test value

Test item (unit)	Before administration (Day 1 of administration)	Day 7 of administration	Day 8 of administration (day of discontinuation)	2 days after discontinuation	7 days after discontinuation (Day 1 of readministration)	Day 5 of readministration (day of discontinuation of readministration)
Blood ammonia (μg/dL)	-	-	201	209	99	175
AST(IU/L)	49	88	-	72	87	54
ALT(IU/L)	65	121	-	94	99	79

Test item (unit)	11 days after discontinuation of readministration	Day 2 of re-readministration (day of discontinuation of re-readministration)	3 days after discontinuation of re-readministration	16 days after discontinuation of re-readministration	24 days after discontinuation of re-readministration
Blood ammonia (μg/dL)	65	160	218	103	74
AST(IU/L)	19	135	219	53	24
ALT(IU/L)	24	128	215	56	22

Concomitant drugs: Clostridium butyricum preparation, lansoprazole, lactulose, magnesium oxide, sulfamethoxazole/trimethoprim, zolpidem tartrate, alprazolam, chlorpromazine hydrochloride, lormetazepam

6 Pembrolizumab (genetical recombination)

Brand name (name of company)	Keytruda Injection 100 mg (MSD K.K.)
Therapeutic category	Other antitumor agent
Indications	·Malignant melanoma ·Unresectable, advanced or recurrent non-small cell lung cancer ·Pre- and postoperative adjuvant therapy for non-small cell lung cancer ·Relapsed or refractory classical Hodgkin lymphoma ·Radically unresectable urothelial carcinoma ·Advanced or recurrent microsatellite instability-high (MSI-High) solid tumours that have progressed after cancer chemotherapy (limited to patients who are refractory or intolerant to standard treatments) ·Radically unresectable or metastatic renal cell carcinoma ·Postoperative adjuvant therapy for renal cell carcinoma ·Recurrent or metastatic head and neck cancer ·Radically unresectable advanced or recurrent oesophageal carcinoma ·Unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer ·PD-L1-positive, hormone receptor-negative and HER2-negative inoperable or recurrent breast cancer ·Pre- and postoperative drug therapy for hormone receptor-negative and HER2-negative breast cancer at high risk of recurrence ·Advanced or recurrent endometrial carcinoma ·Advanced or recurrent, tumour mutational burden-high (TMB-High) solid tumours that have progressed after cancer chemotherapy (limited to patients who are refractory or intolerant to standard treatments) ·Advanced or recurrent cervical cancer ·Locally advanced cervical cancer ·Recurrent or refractory primary mediastinal large B-cell lymphoma ·Unresectable, advanced or recurrent gastric cancer ·Unresectable biliary tract cancer ·Unresectable, advanced or recurrent malignant pleural mesothelioma

PRECAUTIONS (Revised language is underlined.)

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Vasculitis Large-vessel vasculitis, medium-vessel vasculitis, or small-vessel vasculitis [including anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and IgA vasculitis] may occur.
Reference information	Number of cases (for which a causal relationship between the drug and the event is reasonably possible) collected in the PMDA's safety database for drugs Cases involving vasculitis 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 61,000
Japanese market launch: February 2017

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Female 70s	Corpus uteri carcinoma (peritoneal dissemination)	200 mg 1 course every 3 weeks (8 courses in total)	**Large vessel vasculitis**	
				Approximately 3 years before administration	The patient was diagnosed with corpus uteri carcinoma. Histological type: endometrioid carcinoma (G1). TNM classification: T1aN0M0. Staging: Stage IA. Surgical intervention: Total abdominal hysterectomy, bilateral adnexectomy and partial omentectomy were performed.
				101 days before administration	Since peritoneal dissemination appeared, TC (paclitaxel + carboplatin) therapy was initiated.
				56 days before administration	Four courses of TC therapy were completed, but it was discontinued due to progressive disease (PD).
				Day 1 of administration	A combination therapy of pembrolizumab (genetical recombination) and lenvatinib mesilate was initiated.
				Day 67 of administration	The fourth course of pembrolizumab (genetical recombination) was administered. A contrast-enhanced CT was performed to assess the therapeutic effect. The peritoneal dissemination had decreased in size, and the patient was determined to have a partial response (PR). There were no other particular findings. Around the same time, malaise, in addition to myalgia of the lower extremities and claudication of the lower extremities possibly caused by vascular stenosis, appeared. A blood test showed a high CRP level of 3.54 mg/dL. Treatment was continued due to PR, but symptoms such as myalgia of the lower the extremities persisted although they differed in severity. Malaise, myalgia of the lower extremities, and claudication of the lower extremities were symptoms suggestive of large vessel vasculitis. However, a contrast-enhanced CT revealed no vascular wall hypertrophy, and it was not clear whether large vessel vasculitis had developed at this point or not.
				Day 151 of administration: (day of discontinuation)	The eighth course of pembrolizumab (genetical recombination) was administered. Although the symptoms persisted, the clinical course was carefully monitored because CRP did not worsen. CRP was 5.39 mg/dL at the start of the eighth course, showing an increasing tendency of CRP. A contrast-enhanced CT was performed to assess the therapeutic effect. The peritoneal dissemination had disappeared, and no enlarged lymph nodes were observed. Arterial wall thickening from the abdominal aorta to the bilateral common iliac arteries was newly observed.

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
				35 days after discontinuation	The patient was admitted to the rheumatology department for further examination and treatment. CRP and CA125 were high at 8.41 mg/dL and 71.6 U/mL, respectively. Myalgia was noted, but CK was within the normal range. An immunoserological test was also negative for various items including antinuclear antibody and IgG4. Periarterial dissemination around the artery, IgG4-related periaortic inflammation, and giant cell arteritis were considered as a differential diagnosis that could show aortic wall hypertrophy. No enlarged lymph nodes adjacent to the artery were observed, and there were no findings strongly suggestive of disseminated lesions. There was no increase in IgG or IgG4 levels, and IgG4-related periaortic inflammation was also unlikely. On PET-CT, FDG uptake in the area with arterial wall thickening was also observed, leading to a diagnosis of large vessel vasculitis as an irAE. Pembrolizumab (genetical recombination) was discontinued, and it was switched to monotherapy with lenvatinib mesilate. Since vascular wall thickening was observed in the region extending from the abdominal aorta to the bilateral common iliac arteries, there was a risk of complications such as intestinal ischaemia. Therefore, this was managed according to the management of Grade 4 as a condition requiring emergency treatment. [Blood test results on admission] Serum: WBC 6,500/μL. Biochemistry: CRP 8.41 mg/dL, CK 28 U/L, creatinine 0.67 mg/dL. Immunoserology: Antinuclear antibody 40 folds, MPO-ANCA <1.0, PR3-ANCA <1.0, IgG 1,406 mg/dL, IgG4 76.5 mg/dL, syphilis RPR negative, syphilis TPLA negative, NT-proBNP 174 pg/mL, troponin T 0.0008 ng/dL, CA125 71.6 U/mL. [PET-CT findings] A contrast-enhanced CT showed FDG uptake corresponding to the wall thickening of the vessel wall. [Temporal artery biopsy findings] There were no pathological findings suggestive of giant cell arteritis.
				40 days after discontinuation	Administration of prednisolone 50 mg/day was initiated for large vessel vasculitis.
				41 days after discontinuation	CRP decreased to 5.09 mg/dL on Day 1 after the start of treatment.
				42 days after discontinuation	All symptoms improved on Day 2 after the start of treatment. Subsequent blood tests also showed normal CRP. Lenvatinib mesilate could be continued.

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
				45 days after discontinuation	CRP was 0.64 mg/dL.
				47 days after discontinuation	CRP was 0.42 mg/dL.
				61 days after discontinuation	The dose of prednisolone was reduced to 40 mg/day.
				71 days after discontinuation	A contrast-enhanced CT performed 2 months later showed improvement of wall thickening of the large vessel.
				83 days after discontinuation	The dose of prednisolone was reduced to 30 mg/day.
				104 days after discontinuation	The dose of prednisolone was reduced to 25 mg/day.
				184 days after discontinuation	The dose of prednisolone was reduced to 10 mg/day.
				213 days after discontinuation	Peritoneal dissemination relapsed, and administration of lenvatinib mesilate was discontinued due to disease progression. Treatment was terminated. After that, methotrexate 6 mg/week was concomitantly used, and prednisolone was continued after tapering to 0.2 mg/kg/day.
				214 days after discontinuation	Large vessel vasculitis was resolving. Large vessel vasculitis subsequently remitted.
	Concomitant drugs: Lenvatinib mesilate				

Case summary

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
2	Male 70s	Squamous cell carcinoma of lung (hypertension, diabetes mellitus, metastases to left adrenal gland/ischium, obstructive pneumonia)	200 mg 1 course every 3 weeks (3 courses in total)	**Immune-related adverse event (irAE) IgA vasculitis**	
				44 days before administration	Prior to the start of chemotherapy, the patient was hospitalized for obstructive pneumonia, and his Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score was 2. Antimicrobial therapy was administered for obstructive pneumonia.
				30 days before administration	Obstructive pneumonia was resolving.
				29 days before administration	The first course of carboplatin plus paclitaxel (albumin-bound type) was initiated as the first-line therapy for squamous cell carcinoma of the lung (cT4N2M1c stage IVB, PD-L1 expression 10%-24%).
				Day 1 of administration	Since ECOG-PS improved, administration of pembrolizumab (genetical recombination) was also initiated from the second course.
				Day 55 of administration (day of discontinuation)	The fourth course was administered. (Pembrolizumab [genetical recombination] was administered for the third course).
				1 day after discontinuation	CRP was 3.78 mg/dL.
				5 days after discontinuation	Pyrexia persisted, and the patient was admitted to the hospital for further examination. Recurrence of obstructive pneumonia was suspected, and amoxicillin hydrate/clavulanate potassium (AMPC/CVA) was initiated. [Physical conditions on admission] Consciousness alert, ECOG-PS 1, body temperature 37.7°C, blood pressure 123/75 mmHg, pulse rate 92 beats/min, respiratory rate 16 breaths/min, SpO_2 97% (room air), no decrease in oxygenation. Chest: Breath sounds decreased over the dorsal aspect of the left lung. A chest CT scan showed no increase in the mass shadow in the left hilar region, but the findings were suggestive of peripheral obstructive pneumonia. CRP was 4.44 mg/dL.
				8 days after discontinuation	CRP was 8.91 mg/dL. Administration of ampicillin sodium/sulbactam sodium (ABPC/SBT) was initiated. [Blood/urine test findings] (Blood counts) WBC: 7,900/μL, Neut: 71.2%, Lym: 15.8%, Eos: 4.3%, Baso: 0.6%, Mono: 8.1%, RBC: 232 X 10,000/μL, Hb: 7.3 g/dL, Plt: 37.9 X 10,000/μL; (Biochemical) ALB: 2.8 g/dL, LDH: 157 U/L, BUN: 19.9 mg/dL, Cre: 1.12 mg/dL, Na: 143 mmol/L, K: 4.8 mmol/L, CRP: 8.91 mg/dL; (coagulation) PT-INR: 1.04, APTT: 38.6 seconds, D-dimer: 2.4 μg/mL; (Urine analysis) opacity: (-), occult blood: (-), protein qualitative: (-), sediment white blood cells: <1 HPF, sediment red blood cells: <1 HPF.
				12 days after discontinuation	CRP was 5.47 mg/dL.

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
				Approximately 13 days after discontinuation	Multiple purpura on the extremities (Grade 3) and joint swelling of the fingers developed. Purpura was observed not only on the lower extremities but also on the thighs and abdomen. Therefore, an irAE was suspected, and a skin biopsy of the lower extremities was performed. Administration of ceftriaxone sodium hydrate (CTRX) was initiated.
				14 days after discontinuation	CRP was 8.83 mg/dL.
				17 days after discontinuation	Symptoms of diarrhoea and abdominal pain (Grade 3) also developed. CRP was 9.02 mg/dL.
				21 days after discontinuation	Laboratory tests showed increased WBC (11,300/μL), CRP (17.66 mg/dL), BUN (30.3 mg/dL), and Cre (3.35 mg/dL), and proteinuria and haematuria were observed. In addition, serum IgA was elevated (396 mg/dL). A CT scan showed intestinal oedema and ascites. The skin biopsy specimen showed neutrophil-dominated inflammatory cell infiltration from the small vessel wall to the surrounding tissues, suggesting leukocytoclastic vasculitis. Immunofluorescence staining showed granular IgA and C3 deposition in the vessel wall. Therefore, the patient was diagnosed with irAE IgA vasculitis. The symptoms such as purpura, joint swelling, acute kidney injury, and ascites were considered to be due to irAE IgA vasculitis. Steroid pulse therapy with intravenous methylprednisolone (1,000 mg/day) was initiated. The symptoms promptly disappeared, and the Cre level improved. [Blood/urine test findings] (Blood counts) WBC: 11,300/μL, Neut: 74.4%, Lym: 17.6%, Eos: 1.3%, Baso: 0.4%, Mono: 6.3%, RBC: 333 X 10,000/μL, Hb: 9.9 g/dL, Plt: 36.3 X 10,000/μL; (Biochemical) ALB: 1.9 g/dL, BUN: 30.3 mg/dL, Cre: 3.35 mg/dL, eGFR: 15 mL/min/1.73 m^2, Na: 137 mmol/L, K: 4.3 mmol/L, CRP: 17.66 mg/dL, IL-6: 980 pg/mL, blood sugar: 130 mg/dL; (Autoantibodies) antinuclear antibody: <40 times, PR3-ANCA: Negative, MPO-ANCA: Negative, IgA: 396 mg/dL; (Urinalysis) opacity: (-), occult blood: 3+, protein qualitative: 4+, sediment white blood cell: 10-19 HPF, sediment red blood cell: 50-99 HPF, granular cast: 20-29 WF, urine β2-MG: <25 μg/L. [Microbiology test findings] (Bacteriological examination) Sputum culture: Negative, urinary pneumococcus: Negative, urinary Legionella: Negative, tuberculosis IFN-γ: Negative, ASO: 45 IU/mL (Virological test) COVID-19 PCR: Negative, CMV antigenemia: Negative, parvovirus IgM: Negative (Fungi-associated) β-D glucan: Negative.
				23 days after discontinuation	CRP was 14.4 mg/dL.

No.	Patient		Daily dose/ Administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
				24 days after discontinuation	The dose of prednisolone was changed to 60 mg/day (1 mg/kg/day).
				25 days after discontinuation	CRP was 4.83 mg/dL.
				28 days after discontinuation	CRP was 1.77 mg/dL.
				30 days after discontinuation	CRP was 1.14 mg/dL.
				31 days after discontinuation	The dose of prednisolone was reduced to 50 mg/day.
				32 days after discontinuation	CRP: 0.86 mg/dL.
				35 days after discontinuation	CRP: 0.54 mg/dL.
				38 days after discontinuation	The dose of prednisolone was reduced to 40 mg/day.
				45 days after discontinuation	The dose of prednisolone was reduced to 30 mg/day.
				52 days after discontinuation	The dose of prednisolone was reduced to 25 mg/day.
				61 days after discontinuation	The dose of prednisolone was reduced to 20 mg/day.
				75 days after discontinuation	The dose of prednisolone was reduced to 15 mg/day.
				89 days after discontinuation	The dose of prednisolone was reduced to 10 mg/day.
				124 days after discontinuation	The dose of prednisolone was reduced to 7.5 mg/day.
				145 days after discontinuation	The dose of prednisolone was reduced to 5 mg/day. The dose of prednisolone was maintained at 5 mg/day, and no aggravation of symptoms was observed.
	Concomitant drugs: Carboplatin, paclitaxel (albumin-bound type), amoxicillin hydrate/potassium clavulanate, ampicillin sodium/sulbactam sodium, febuxostat, candesartan cilexetil, voglibose, mirogabalin besilate, clostridium butyricum preparation, loxoprofen sodium hydrate, esomeprazole magnesium hydrate				

3

Revisions of PRECAUTIONS (No. 362)

This section presents details of revisions to the PRECAUTIONS and brand names of drugs that have been revised in accordance with the Notification dated July 30, 2025.

1 Other hormone preparations (including antihormone preparations), antidiabetic agents

[1] Semaglutide (genetical recombination)
[2] Tirzepatide
[3] Insulin glargine (genetical recombination)/lixisenatide

Brand name	[1] Wegovy Subcutaneous Injection 0.25 mg SD, 0.5 mg SD, 1.0 mg SD, 1.7 mg SD, 2.4 mg SD, 0.25 mg pen 1.0 MD, 0.5 mg pen 2.0 MD, 1.0 mg pen 4.0 MD, 1.7 mg pen 6.8 MD, 2.4 mg pen 9.6 MD, Ozempic Subcutaneous Injection 2 mg, Rybelsus tablets 3 mg, 7 mg, 14 mg (Novo Nordisk Pharma Ltd.) [2] Zepbound Subcutaneous Injection 2.5 mg Ateos, 5 mg Ateos, 7.5 mg Ateos, 10 mg Ateos, 12.5 mg Ateos, 15 mg Ateos, Mounjaro Subcutaneous Injection 2.5 mg Ateos, 5 mg Ateos, 7.5 mg Ateos, 10 mg Ateos, 12.5 mg Ateos, 15 mg Ateos (Eli Lilly Japan K.K.) [3] Soliqua Injection SoloStar (Sanofi K.K.)
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc. (newly added)**	Patients with a medical history of abdominal surgery or ileus Ileus, including intestinal obstruction, may occur.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Ileus Ileus, including intestinal obstruction, may occur. If any abnormalities such as severe constipation, abdominal distension, persistent abdominal pain, or vomiting are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

2 Other antitumor agents

[1] Afatinib maleate
[2] Fulvestrant

Brand name	[1] Giotrif Tablets 20 mg, 30 mg, 40 mg (Nippon Boehringer Ingelheim Co ., Ltd.) [2] Faslodex Intramuscular Injection 250 mg (AstraZeneca K.K.)
11. ADVERSE REACTIONS	Anaphylaxis

11.1 Clinically Significant Adverse Reactions (newly added)	

3 Other antitumor agents

Avelumab (genetical recombination)

Brand name	Bavencio intravenous infusion 200 mg (Merck Biopharma Co., Ltd)
8. IMPORTANT PRECAUTIONS	Hepatic failure, hepatic impairment, hepatitis, and sclerosing cholangitis may occur. Patients should be carefully monitored through periodic liver function tests.
11. ADVERSE REACTIONS	Hepatic failure, hepatic impairment, hepatitis, sclerosing cholangitis
11.1 Clinically Significant Adverse Reactions	Hepatic failure, hepatic impairment accompanied by increased levels of AST, ALT, γ-GTP, bilirubin, etc., hepatitis, and sclerosing cholangitis may occur.

4 Other antitumor agents

Sunitinib malate

Brand name	Sutent Capsule 12.5 mg (Pfizer Japan Inc.) and the others
11. ADVERSE REACTIONS	Hyperammonaemia
11.1 Clinically Significant Adverse Reactions (newly added)	Hyperammonaemia may occur even in the absence of abnormal hepatic function. If disturbed consciousness is observed, measurement of blood ammonia levels should be considered.

5 Other antitumor agents

Pembrolizumab (genetical recombination)

Brand name	Keytruda Injection 100 mg (MSD K.K.)
11. ADVERSE REACTIONS	Vasculitis
11.1 Clinically Significant Adverse Reactions (newly added)	Large-vessel vasculitis, medium-vessel vasculitis, or small-vessel vasculitis [including anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and IgA vasculitis] may occur.

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, 2025)
◎: Products for which EPPV was initiated after June 1, 2025

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiation
◎	Drospirenone[*1] Slinda 28 Tablets	Aska Pharmaceutical Co., Ltd.	June 30, 2025
◎	Purified Vi polysaccharide typhoid vaccine Typhim Vi Syringe for Injection	Sanofi K.K.	June 30, 2025
◎	Guselkumab (genetical recombination)[*2] Tremfya Intravenous Infusion 200 mg, Tremfya Subcutaneous Injection Syringe 100 mg, 200 mg, Tremfya Subcutaneous Injection 200 mg Pen	Janssen Pharmaceutical K.K.	June 24, 2025
◎	Vutrisiran sodium[*3] Amvuttra Subcutaneous Injection 25 mg Syringe	Alnylam Japan K.K.	June 24, 2025
◎	pH4-Treated acidic normal human immunoglobulin (subcutaneous injection), vorhyaluronidase alfa (genetical recombination)[*4] HyQvia 10% S.C. Injection Set 5 g/50 mL, 10 g/100 mL, 20 g/200 mL	Takeda Pharmaceutical Company Limited	June 24, 2025
◎	IncobotulinumtoxinA Xeomin 50 units, 100 units, 200 units for Intramuscular injection	Teijin Pharma Limited	June 24, 2025
◎	Remimazolam besilate[*5] Anerem 50 mg for I.V. Injection	Mundipharma K.K.	June 24, 2025
◎	Maralixibat chloride Livmarli Oral Solution 10 mg/mL	Takeda Pharmaceutical Company Limited	June 12, 2025
◎	pH4-Treated acidic normal human immunoglobulin (subcutaneous injection), vorhyaluronidase alfa (genetical	Takeda Pharmaceutical Company Limited	June 12, 2025

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiation
	recombination) HyQvia 10% S.C. Injection Set 5 g/50 mL, 10 g/100 mL, 20 g/200 mL		
◎	Ivosidenib Tibsovo Tablets 250 mg	Nihon Servier Co., Ltd.	June 2, 2025
	Amivantamab (genetical recombination)[*6] Rybrevant Intravenous Infusion 350 mg	Janssen Pharmaceutical K.K.	May 21, 2025
	Tisotumab vedotin (genetical recombination) Tivdak for Intravenous Infusion 40 mg	Genmab K.K.	May 21, 2025
	Lazertinib mesilate hydrate Lazcluze Tablets 80 mg, 240 mg	Janssen Pharmaceutical K.K.	May 21, 2025
	Guselkumab (genetical recombination)[*7] Tremfya Intravenous Infusion 200 mg, Tremfya Subcutaneous Injection 200 mg Syringe, 200 mg Pen, 100 mg Syringe	Janssen Pharmaceutical K.K.	May 21, 2025
	Mavacamten Camzyos capsules 5 mg, 2.5 mg, 1 mg	Bristol-Myers Squibb K.K.	May 21, 2025
	Acoramidis hydrochloride Beyonttra tablets 400 mg	Alexion Pharma Godo Kaisha	May 21, 2025
	Amivantamab (genetical recombination)*[8] Rybrevant Intravenous Infusion 350 mg	Janssen Pharmaceutical K.K.	May 19, 2025
	Iptacopan hydrochloride hydrate[*9] Fabhalta capsules 200 mg	Novartis Pharma K.K.	May 19, 2025
	Atropine sulfate hydrate[*10] Ryjusea Mini ophthalmic solution 0.025%	Santen Pharmaceutical Co., Ltd.	April 21, 2025
	Garadacimab (genetical recombination) Andembry S.C. Injection 200 mg Pens	CSL Behring K.K.	April 18, 2025
	Brivaracetam Briviact for I.V. injection 25 mg	UCB Japan Co. Ltd.	April 17, 2025
	Tarlatamab (genetical recombination) Imdelltra For I.V. Infusion 1 mg, 10 mg	Amgen K.K.	April 16, 2025
	Tirzepatide[*11] Zepbound Subcutaneous Injection Ateos 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg	Eli Lilly Japan K.K.	April 11,2025
	Letermovir[*12] Prevymis Tablets 240 mg, Prevymis Intravenous Infusion 240 mg	MSD K.K.	March 27, 2025
	Marstacimab (genetical recombination) Hympavzi S.C. Injection 150 mg Pen	Pfizer Japan Inc.	March 24, 2025
	Teclistamab (genetical recombination) Tecvayli Subcutaneous Injection 153 mg, 30 mg	Janssen Pharmaceutical K.K.	March 19, 2025
	Mosunetuzumab (genetical recombination) Lunsumio for Intravenous Infusion 1 mg, 30 mg	Chugai Pharmaceutical Co., Ltd.	March19, 2025

Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiation
Datopotamab deruxtecan (genetical recombination) Datroway for Intravenous Drip Infusion 100 mg	Daiichi Sankyo Co., Ltd.	March 19, 2025
Selexipag Uptravi Tablets for Pediatric 0.05 mg	Nippon Shinyaku Co., Ltd.	March 19, 2025
Ozanimod hydrochloride Zeposia capsules 0.92 mg, Zeposia capsules starter pack	Bristol-Myers Squibb K.K.	March 19, 2025
Tofersen Qalsody Intrathecal injection 100 mg	Biogen Japan Ltd	March 19, 2025
Zanubrutinib Brukinsa capsules 80 mg	BeiGene Japan GK	March 19, 2025
Patiromer sorbitex calcium Veltassa 8.4 g powder for suspension (single-dose package)	Zeria Pharmaceutical Co., Ltd.	March 17, 2025
Flortaucipir (^{18}F) Tauvid Injection	PDRadiopharma Inc.	March 3, 2025
Insulin Icodec (genetical recombination) Awiqli injection FlexTouch 300 units, 700 units	Novo Nordisk Pharma Ltd.	January 30, 2025
Articaine hydrochloride/adrenaline bitartrate Septocaine Combination Injection Cartridge	GC SHOWAYAKUHIN CORPORATION	January 21, 2025
Amifampridine phosphate Firdapse Tablets 10 mg	DyDo Pharma, Inc.	January 15, 2025

*1 Contraception

*2 Treatment of moderate to severe active Crohn's disease (only in patients who have had an inadequate response to conventional treatments)

*3 Transthyretin cardiac amyloidosis (wild type and mutant type)

*4 Slowing the progression of motor function decline in chronic inflammatory demyelinating polyradiculoneuritis and multifocal motor neuropathy (when improvement in muscle weakness is observed)

*5 Sedation during gastrointestinal endoscopy

*6 Coadministration with lazertinib mesilate hydrate for unresectable, advanced or recurrent *EGFR* mutation-positive non-small cell lung cancer

*7 Maintenance therapy for moderate to severe ulcerative colitis (only in patients who have had an inadequate response to conventional treatments)

*8 Coadministration with carboplatin and pemetrexed sodium hydrate for unresectable, advanced or recurrent *EGFR* mutation-positive non-small cell lung cancer

*9 C3 nephropathy

*10 Slowing the progression of myopia

*11 Treatment of obesity
The use is limited to patients with either hypertension, dyslipidaemia, or type 2 diabetes mellitus who have not sufficiently responded to treatment with dietary and exercise therapy and who fall under 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

*12 Addition of a pediatric dosage for the indication below:
Prophylaxis of cytomegalovirus disease for the following:
* Allogeneic haematopoietic stem cell transplantation
* Organ transplantation