Pharmaceuticals and Medical Devices Safety Information

No. 397

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Available information is listed here

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Pharmaceuticals and Medical Devices Safety Information

No. 397

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

[Outline of Information]

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

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

Please utilize the Report Reception Site for reporting.
(This service is only available in Japanese.)
https://www.pmda.go.jp/safety/reports/hcp/0002.html

Abbreviations

ADEM	Acute Disseminated Encephalomyelitis
ADR	Adverse Drug Reaction
ECMO	Extracorporeal Membrane Oxygenation
EPPV	Early Post-marketing Phase Vigilance
FiO_2	Fraction of Inspiratory Oxygen
HSB	Health Service Bureau
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
pCO_2	Partial Pressure of Carbon Dioxide
PEEP	Positive End-Expiratory Pressure
PMDA	Pharmaceuticals and Medical Devices Agency
PMD Act	Act on Securing Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices
pO_2	Partial Pressure of Oxygen
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
PV Law	Preventive Vaccination Law
SOC	System Organ Class

1
Suspected Adverse Reactions to Influenza Vaccines in the 2021 Season

1. Introduction

This section describes the status of instances of suspected adverse reactions to influenza vaccines reported from October 1, 2021 through March 31, 2022 (hereinafter referred to as the "2021 season").

Medical institutions are required to report to MHLW when they encounter symptoms that they decide meet the Suspected Adverse Reaction Reporting Criteria for influenza vaccines regardless of causality. Reports by medical institutions, together with those by MAHs, are compiled and evaluated by PMDA. For serious cases including patient mortalities, PMDA performs causality assessment and/or considers the necessity of safety measures in consultation with experts.

Joint meetings of the Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council and the Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (hereinafter referred to as the "Joint Meeting") are convened periodically for the purpose of investigating and reviewing these reports of suspected adverse reactions to influenza vaccines and to discuss the necessity of safety measures[1)2)].

2. Reports of Suspected Adverse Reactions to Influenza Vaccines (2021 season)

(1) Numbers and frequencies of suspected adverse reactions reported

Table 1 shows the numbers of reported suspected adverse reactions to the influenza vaccines and frequencies calculated from the estimated numbers of vaccinated persons based on the number of vaccines distributed to medical institutions.

Table 1 Numbers of suspected adverse reactions reported and estimated number of vaccinated persons

	Reports by MAHs (serious reports)*		Reports by medical institutions**		
Estimated number of vaccinated persons (number of vaccinations)	Number of serious cases reported (frequency)	Number of patient mortalities reported	Number of reports (frequency)	Number of serious cases reported (frequency)	Number of patient mortalities reported
51 946 849 (as of March 31, 2022)	16 (0.00003%)	3 (0.00001%)	77 (0.00015%)	34 (0.00007%)	4 (0.00001%)

* Reports by MAHs were of cases determined to be "serious" in accordance with Article 68-10-1 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices (PMD Act). Reports by MAHs may duplicate some cases reported by medical institutions, and duplicated cases were added up as reported by medical institutions.

** Reports by medical institutions were submitted in accordance with Article 12-1 of the Preventive Vaccination Law (PV Law) or Article 68-10-2 of the PMD Act.

(2) Reports of suspected adverse reactions by sex and age group

The numbers of reported suspected adverse reactions to influenza vaccines are shown by sex and age group in Table 2 and Table 3, respectively.

Table 2 Number of reports by sex

Sex	Number of Reports by MAHs	Number of reports by medical institutions
Male	9	35
Female	5	42
Unknown	2	0
Total	16	77

Table 3 Number of reports by age group

Age group	Number of Reports by MAHs		Number of reports by medical institutions		
	Number of serious cases reported		Number of reports	Number of serious cases reported	
		Number of patient mortalities reported			Number of patient mortalities reported
0 - 9	3	0	37	18	0
10 - 19	0	0	7	3	0
20 - 29	0	0	4	1	0
30 - 39	0	0	3	0	0
40 - 49	1	0	3	1	0
50 - 59	1	0	3	1	0
60 - 69	0	0	6	1	0
70 - 79	3	1	5	3	2
80 or older	4	1	9	6	2
Unknown	4	1	0	0	0
Total	16	3	77	34	4

(3) Details of reported symptoms

Suspected adverse reactions to influenza vaccines reported during the 2021 season are outlined by System Organ Class (SOC) in the right-hand side columns of Table 4. There were no increases in the numbers and frequencies of adverse reactions reported compared with the 2020 season (October 1, 2020 to September 30, 2021).

A total of 7 cases of post-vaccination deaths were reported for this season. The assessment by experts determined that the causality between the vaccination and death could not be assessed due to lack of information for these cases.

A total of 3 cases (Note 1) of possible Guillain-Barré syndrome or acute disseminated encephalomyelitis (ADEM) were reported for this season. The assessment by experts determined that a causal relationship between the respective diseases and vaccination was reasonably possible.

A total of 9 cases (Note 2) were reported as possible anaphylaxis. Of these, 3 cases were assessed as Level 3 or higher anaphylaxis using the Brighton Criteria (including 3 serious cases). Regarding the number of reports from MAHs by manufacturing lot, there were no distinct concentrations of reports of anaphylaxis found on specific lots.

At the Joint Meeting held in July, 2022, it was concluded that there were no new concerns regarding safety of the vaccines, including other reported symptoms than anaphylaxis, with no safety measures such as revision of package inserts required at present but reporting of suspected adverse reactions and their details should be carefully monitored.

Note 1) Cases reported with the symptom name “Guillain-Barré syndrome” or “ADEM.”
Note 2) Cases reported with the symptom name “anaphylactic reaction,” “anaphylactic shock,” “anaphylactoid reaction,” or “anaphylactoid shock.”

Table 4 Comparison of the number of suspected adverse reaction reports between the 2020 and 2021 seasons (by SOC)

	2020 season†		2021 season††	
SOC of symptom	Reports by MAHs	Reports by medical institutions (serious cases)	Reports by MAHs	Reports by medical institutions (serious cases)
Gastrointestinal disorders	8	9	1	7
General disorders and administration site conditions	38	26	5	23
Infections and infestations	4	16	1	4
Haepatobiliary disorders	8	4	2	2
Eye disorders	1	2	1	0
Musculoskeletal and connective tissue disorders	5	16	1	5
Blood and lymphatic system disorders	3	7	1	3
Vascular disorders	0	5	1	1
Respiratory, thoracic and mediastinal disorders	7	2	0	5
Ear and labyrinth disorders	1	1	0	0
Injury, poisoning and procedural complications	0	1	0	0
Cardiac disorders	4	3	0	2
Nervous system disorders	23	54	1	14
Renal and urinary disorders	12	5	3	7
Metabolic and nutritional disorders	2	2	1	0
Endocrine disorders	6	0	0	0
Skin and subcutaneous tissue disorders	11	18	3	3
Immune system disorders	10	9	1	8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0	0	0
Investigations	6	2	3	3
Total	150	182	25	87

† Reported from October 1, 2020 to September 30, 2021
†† Reported from October 1, 2021 to March 31, 2022

3. Future safety measures

As detailed in the Reporting Suspected Adverse Reactions for Routine Vaccination, etc.[3)] notification, medical institutions are urged to promptly report when they encounter symptoms that they believe meet the Suspected Adverse Reaction Reporting Criteria even if the causality is unclear.

In addition to the conventional reporting by fax, electronic reporting is available through the

website since April 1, 2021.
[Report Reception Site (electronic report system)]
https://www.pmda.go.jp/safety/reports/hcp/0002.html (only in Japanese)

MHLW/PMDA will continue their efforts to gather information concerning the safety of influenza vaccines including suspected adverse reaction reports, etc. and to implement safety measures based on such information. Continued cooperation is requested in alerting vaccine recipients to adverse reactions and reporting them when suspected.

[References]

1) MHLW: Material 2-25 for the Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council (the 78th meeting) and the 2022 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (the 1st meeting) (Joint Meeting), Reports of Suspected Adverse Reactions to Influenza Vaccines
https://www.mhlw.go.jp/content/10601000/000936155.pdf (only in Japanese)

2) MHLW: Material 2-22 for the Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council (the 81st meeting) and the 2022 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (the 6th meeting) (Joint Meeting), Reports of Suspected Adverse Reactions to Influenza Vaccines
https://www.mhlw.go.jp/content/10601000/000962158.pdf (only in Japanese)

3) Partial Amendment of Reporting Suspected Adverse Reactions for Routine Vaccinations, etc. dated October 24, 2022, Joint HSB Notification No. 1024-5 and PSEHB Notification No.1024-1, by the Director-General of Health Service Bureau and by the Director-General of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labor and Welfare
https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/hukuhannou_houkoku/kanrentuuti.html (only in Japanese)

Report form
https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/hukuhannou_houkoku/dl/r04youshiki_02.pdf (only in Japanese)

Entry instructions
https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/hukuhannou_houkoku/dl/r04youshiki_03.pdf (only in Japanese)

Report entry application (National Institute of Infectious Diseases)
http://www.nih.go.jp/niid/ja/vaccine-j/6366-vaers-app.html (only in Japanese)

Reference: Suspected Adverse Reaction Reporting Criteria
<Routine vaccination>

Symptoms	Time to onset after inoculation
Anaphylaxis	4 hours
Hepatic impairment	28 days
Interstitial pneumonia	28 days
Acute disseminated encephalomyelitis (ADEM)	28 days
Acute generalised exanthematous pustulosis (AGEP)	28 days
Guillain-Barré syndrome	28 days
Convulsion	7 days
Vasculitis	28 days
Thrombocytopenic purpura	28 days
Optic neuritis	28 days
Myelitis	28 days
Asthmatic attack	24 hours
Nephrotic syndrome	28 days
Encephalitis or encephalopathy	28 days
Oculomucocutaneous syndrome	28 days
Other reactions (symptoms suspected to be associated with the vaccination and either (1) requiring hospital admission or (2) resulting in, or associated with a risk of death or persistent incapacity)	Time frame in which the event was considered by the physician to be associated with the vaccination

Except for “other reactions,” any event occurring within the specified time frame is subject to mandatory reporting to MHLW regardless of causality according to the PV Law and related rules.

<Voluntary vaccination>

Adverse reactions or infections associated with voluntary vaccinations should be reported when reporting is considered necessary to prevent the occurrence and spread of health hazards. Refer to the following for specific cases subject to reporting. Adverse reactions and infections for which causality with vaccinations is unclear may also be subject to reporting.

(1) Death
(2) Disability
(3) Events that may result in death
(4) Events that may result in disability
(5) Symptoms that require admission or prolonged hospitalization at medical institutions for treatment [excluding events in (3) and (4)]
(6) Serious events corresponding to those in items (1) to (5)
(7) Congenital diseases or anomalies in the next generation
(8) Onset of infections suspected of being caused by use of the applicable pharmaceutical
(9) Onset of unknown events which are not mild and could not be predicted based on the package insert, other than those listed in (1) to (8)

2

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated November 16, 2022, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 Roxadustat

Brand name (name of company)	Evrenzo Tablets 20 mg, 50 mg, 100 mg (Astellas Pharma Inc.)
Therapeutic category	Agents affecting metabolism, n.e.c. (not elsewhere classified)
Indications	Nephrogenic anaemia

PRECAUTIONS (revised language is underlined)

[Under new instructions]

8. IMPORTANT PRECAUTIONS (newly added)	Central hypothyroidism may occur during administration of this drug. Cases in which central hypothyroidism developed approximately 2 weeks after initiation of administration have been reported. Patients should be carefully monitored through methods including periodical thyroid function tests (measurement of thyroid-stimulating hormone (TSH), free T3, free T4) during treatment with this drug.
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Central hypothyroidism Central hypothyroidism, in which the blood TSH level is within the normal range or low, may occur. If symptoms or signs appear, appropriate measures should be taken such as discontinuation of this drug and administration of thyroid hormone preparations as necessary.
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) reported during the previous approximately 3-year period Cases involving central hypothyroidism: 9 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 42 000 Japanese Market launch: November 2019

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>1</td><td>Male
80s</td><td>Nephrogenic anaemia (chronic renal failure, hypothyroidism, secondary hyperparathyroidism, carnitine deficiency, hyperuricaemia, hyperlipidaemia, chronic gastritis, chronic cardiac failure, large intestine angiodysplasia, iron deficiency anaemia, cutaneous pruritus, insomnia, chronic constipation)</td><td>100 mg
22 days</td><td colspan="2">Hypothyroidism
Before administration: The patient was treated with levothyroxine sodium hydrate (25 μg) due to hypothyroidism.
Day 1 of administration: Darbepoetin alfa (100 μg/week) was switched to roxadustat (100 mg, 3 times a week) for renal anaemia in the dialysis period.
12 days after administration: Thyroid stimulation hormone (TSH) rapidly declined to 0.12 μIU/mL, and free thyroxine (FT4) to 0.56 ng/dL. Aggravation of hypothyroidism developed.
21 days after administration (day of discontinuation): The patient’s inappetence and decreased weight gain were noted. Also, yellowing was noted on the dialyzer at the completion of dialysis. Administration of roxadustat was discontinued.
2 days after discontinuation: Total bilirubin was elevated, and a CT scan revealed biliary sludge. Jaundice and hepatic impairment developed.
5 days after discontinuation: Total bilirubin was further elevated, and the patient could hardly eat any food. Therefore, he was admitted to the hospital for a follow-up and a detailed examination.
6 days after discontinuation: Administration of atorvastatin calcium hydrate, allopurinol, fexofenadine hydrochloride, esomeprazole magnesium hydrate was discontinued since drug-induced hepatic impairment was suspected.
7 days after discontinuation: The dose of levothyroxine sodium hydrate was increased (37.5 μg).
8 days after discontinuation: The patient’s appetite improved, and he ate all of the meals. He recovered from inappetence.
33 days after discontinuation: The patient’s jaundice and hepatic impairment recovered.
47 days after discontinuation: Aggravation of the patient’s hypothyroidism recovered.
62 days after discontinuation: The patient was discharged from the hospital.</td></tr>
<tr><td></td><td colspan="5">Laboratory test value
<table>
<tr><th></th><th>23 days before admin.</th><th>2 days before admin.</th><th>12 days after admin.</th><th>19 days after admin.</th><th>2 days after discon-tinuation</th><th>5 days after discon-tinuation</th><th>12 days after discon-tinuation</th><th>19 days after discon-tinuation</th><th>33 days after discon-tinuation</th><th>47 days after discon-tinuation</th></tr>
<tr><td>TSH (μIU/mL)</td><td>14.85</td><td>—</td><td>0.12</td><td>0.10</td><td>—</td><td>—</td><td>—</td><td>5.73</td><td>—</td><td>3.67</td></tr>
<tr><td>FT4 (ng/dL)</td><td>0.94</td><td>—</td><td>0.56</td><td>0.39</td><td>—</td><td>—</td><td>—</td><td>0.83</td><td>—</td><td>0.83</td></tr>
<tr><td>Hb (g/dL)</td><td>8.4</td><td>9.2</td><td>11.0</td><td>12.4</td><td>12.6</td><td>14.2</td><td>13.7</td><td>12.9</td><td>11.2</td><td>11.3</td></tr>
<tr><td>T-BiL (mg/dL)</td><td>—</td><td>0.67</td><td>—</td><td>—</td><td>3.73</td><td>4.15</td><td>2.04</td><td>—</td><td>1.18</td><td>—</td></tr>
<tr><td>D-BiL (mg/dL)</td><td>—</td><td>—</td><td>—</td><td>—</td><td>2.71</td><td>3.11</td><td>1.15</td><td>—</td><td>—</td><td>—</td></tr>
<tr><td>AST (IU/L)</td><td>—</td><td>33</td><td>—</td><td>—</td><td>32</td><td>36</td><td>38</td><td>—</td><td>18</td><td>—</td></tr>
<tr><td>ALT (IU/L)</td><td>—</td><td>20</td><td>—</td><td>—</td><td>20</td><td>20</td><td>25</td><td>—</td><td>13</td><td>—</td></tr>
<tr><td>Al-P (IU/L)</td><td>—</td><td>378</td><td>—</td><td>—</td><td>310</td><td>314</td><td>290</td><td>—</td><td>332</td><td>—</td></tr>
<tr><td>γ-GTP (IU/L)</td><td>—</td><td>65</td><td>—</td><td>—</td><td>35</td><td>30</td><td>33</td><td>—</td><td>53</td><td>—</td></tr>
</table></td></tr>
<tr><td></td><td colspan="5">Concomitant drugs: Levothyroxine sodium hydrate, alfacalcidol, levocarnitine, allopurinol, atorvastatin calcium hydrate, rebamipide, esomeprazole magnesium hydrate, bisoprolol fumarate, ferrous fumarate, fexofenadine hydrochloride, nalfurafine hydrochloride, brotizolam, lactulose</td></tr>
</table>

2 Preparations containing hydrochlorothiazide
[1] hydrochlorothiazide
[2] losartan potassium/hydrochlorothiazide
[3] candesartan cilexetil/hydrochlorothiazide
[4] valsartan/hydrochlorothiazide

Brand name (name of company)	[1] Hydrochlorothiazide Tablets 12.5 mg "Towa," Tablets 25 mg "Towa," Hydrochlorothiazide OD Tablets 12.5 mg "Towa" (Towa Pharmaceutical Co., Ltd.) [2] Preminent Tablets LD, HD (Organon K.K.), and the others [3] Ecard Combination Tablets LD, HD (Teva Takeda Yakuhin Ltd.), and the others [4] Co-Dio combination Tablets MD, EX (Novartis Pharma K.K.), and the others
Therapeutic category	Diuretics, antihypertensives
Indications	[1] Hypertension (essential, renal, etc.), malignant hypertension, cardiac induced oedema (congestive heart failure), renal induced oedema, hepatic induced oedema, premenstrual tension, oedema caused by drugs (corticosteroids, phenylbutazone, etc.) [2]-[4] Hypertension

PRECAUTIONS (revised language is underlined)

[Under old instructions]

Adverse reactions	Interstitial pneumonia, pulmonary oedema, acute respiratory distress syndrome:
Clinically Significant Adverse Reactions	Interstitial pneumonia, pulmonary oedema may occur. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken. In addition, it has been reported that acute respiratory distress syndrome developed within minutes to hours after taking hydrochlorothiazide.

[Under new instructions]

11. ADVERSE REACTIONS	Interstitial pneumonia, pulmonary oedema, acute respiratory distress syndrome
11.1 Clinically Significant Adverse Reactions	Interstitial pneumonia, pulmonary oedema may occur. In addition, it has been reported that acute respiratory distress syndrome developed within minutes to hours after taking hydrochlorothiazide.
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) reported during the previous approximately 3-year period [1]-[4] Cases involving acute respiratory distress syndrome: 0 Number of patients using the drug as estimated by the MAH during the previous 1-year period: [1] Approximately 57 040 [2] Approximately 63 000 [3] Approximately 36 711 [4] Combination Tablets MD: Approximately 8 568, Combination Tablets EX: Approximately 24 452 Japanese market launch: [1] Tablets 12.5 mg: June 2012, Tablets 25 mg: April 1978, OD Tablets 12.5 mg: December 2013 [2] Tablets LD: December 2006, Tablets HD: April 2014 [3] March 2009 [4] March 2009

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Male 50s	Hypertension (unknown)	unknown (unknown)	**Acute respiratory distress syndrome**	
				4 years before	The patient was additionally administered with hydrochlorothiazide for hypertension. On the same day, nausea and shortness of breath developed. He was admitted to another hospital and intubated. A chest X-ray revealed white turbidity in bilateral lung fields, and he was diagnosed with acute respiratory distress syndrome. For 5 days, he remained intubated and was treated for *Streptococcus pneumoniae.* Later, he was discharged from the hospital.
				2 years before	Antihypertensive drug (combination drug: Name of drug is unknown.) was administered. Chills and cyanosis developed after the administration, and he was admitted to the intensive care unit in another hospital. A chest X-ray revealed diffuse infiltration in bilateral lung fields, for which a broad-spectrum antibiotic was administered. He was discharged from the hospital 3 days later.
				Day 1 of administration	Hydrochlorothiazide was administered for blood pressure control.
				30 minutes after administration	The patient felt poorly and developed progressive shortness of breath. He was transported to another hospital by ambulance. Progressive dyspnoea, hypoxaemia, and hypotension were observed, and he was orally intubated. Pulse oximetry showed the value ranging from 60 to 70%, although the fraction of inspiratory oxygen (FiO_2) was 100% and positive end-expiratory pressure (PEEP) was high. Pulmonary oedema was suspected, and administration of norepinephrine and intravenous furosemide was initiated. The patient was transferred to the emergency department of this hospital by an air ambulance. Cardiac arrest occurred while in the air ambulance, but he was resuscitated. Immediately after emergency transportation, heart rate was 136 beats/min, blood pressure 125/90 mmHg, and pulse oximetry 79%. Sinus tachycardia accompanied by non-specific ST segment and T wave inversion was observed. The value of arterial blood gas was 7.04 for pH, 82 mmHg for partial pressure of carbon dioxide (pCO_2), and 65 mmHg for partial pressure of oxygen (pO_2). Norepinephrine, vasopressin, epinephrine and calcium chloride were administrated, but progressive and refractory hypotension developed. Although FiO_2 was 100% and PEEP was high, pulse oximetry showed the value ranging from 45 to 82%. The value of arterial blood gas was 7.05 for pH, 47 mmHg for pCO_2, and 49 mmHg for pO_2, indicating metabolic acidosis. Within 15 minutes after initiating extracorporeal membrane oxygenation (ECMO), pulse oximetry showed a value greater than 88%. The value of arterial blood gas was 7.29 for pH, 48 mmHg for

					pCO_2, and 110 mmHg for pO_2, showing improvements in acidosis and oxygenation. The patient was transferred to the intensive care unit. A high-dose steroid and broad-spectrum antibiotic were administered. A chest X-ray revealed bilateral interstitial infiltration, which was diagnosed as pulmonary oedema. ECMO was continued for 5 days. The patient was discharged from the hospital. The patient was examined as an outpatient, showing recovery to baseline. It was considered probable that severe acute respiratory distress syndrome was caused by hydrochlorothiazide-induced pulmonary oedema judging from the past clinical courses and current symptoms.
				12 days after administration 1 month after hospital discharge	
	Concomitant drugs: Unknown Note: Jansson PS, et al. J Emerg Med. 2018; 55: 836-40.				

3 Imatinib mesilate

Brand name (name of company)	Glivec Tablets 100 mg (Novartis Pharma K.K.), and the others
Therapeutic category	Other antitumor agents
Indications	·Chronic myeloid leukaemia ·KIT (CD117)-positive gastrointestinal stromal tumor ·Philadelphia chromosome-positive acute lymphocytic leukaemia ·The following FIP-1-like-1-platelet-derived growth factor receptor alpha (FIP1L1-PDGFRα)-positive diseases: Hypereosinophilic syndrome, chronic eosinophilic leukaemia

PRECAUTIONS (revised language is underlined)

[Under old instructions]

Adverse Reactions Clinically Significant Adverse Reactions (newly added)	Thrombotic microangiopathy: Thrombotic microangiopathy may occur. If anaemia accompanied by schizocytes, thrombocytopenia, renal impairment, etc. are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

[Under new instructions]

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Thrombotic microangiopathy If anaemia accompanied by schizocytes, thrombocytopenia, renal impairment, etc. 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 event is reasonably possible) reported during the previous approximately 3-year period Cases involving thrombotic microangiopathy: 0 Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 5 300 Japanese market launch: July 2005

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
1	Male 30s	Chronic blast crisis in myelogenous leukaemia (none)	400 mg 41 days ↓ 600 mg 25 days	**Thrombotic microangiopathy** Approximately 3 years ago: The patient visited the hospital after a medical checkup revealed an increased white blood cell count. He was diagnosed with chronic myeloid leukaemia (chronic phase). He started taking imatinib mesilate, but discontinued it at his own discretion. Approximately 7 months before administration: The patient was hospitalized for lymphoid crisis. Approximately 1 month before administration: Chronic myeloid leukaemia was in a chronic phase after chemotherapy, but returned to an acute phase. Day 1 of administration: Administration of imatinib mesilate 400 mg was initiated. Day 42 of administration: The dose of imatinib mesilate was increased to 600 mg. Day 62 of administration: The patient was hospitalized for cord blood transplant. BUN 12.3 mg/dL, Cr 0.78 mg/dL Day 66 of administration (Day of discontinuation): The final dose of imatinib mesilate was administered. 1 day after discontinuation: Acute renal failure developed. The patient complained of left-sided abdominal pain. A glycerin enema of 110 mL was administered. Due to persistent abdominal pain, intramuscular pentazocine 15 mg and intravenous butylscopolamine 1/2 ampule were administered. Abdominal ultrasonography showed a small intestine enlargement. Ileus was suspected. An abdominal CT was performed (simple + contrast). A simple CT revealed suspected inflammation of bilateral kidneys. There were no other findings that could have caused the abdominal pain. According to the patient, he had not urinated at all since early morning. He did not urinate even though he had the urge to urinate. A urinary catheter was inserted, but he was completely anuric. A loading dose of 500 mL of lactated Ringer's solution was administered. In the afternoon of the same day, BUN rose to 18.0 mg/dL and Cr to 2.35 mg/dL. He continued to receive supplemental fluids, but was completely anuric. Intravenous furosemide 20 mg, 40 mg, and 100 mg were administered approximately every 3 hours from the night of the same day to the next morning. 2 days after discontinuation: BUN rose to 28.4 mg/dL and Cr to 4.68 mg/dL. Marked generalised oedema was noted. Haemodialysis was performed, and 1 800 mL of water was removed. The patient's anuria persisted thereafter. 3 days after discontinuation: BUN rose to 42.3 mg/dL and Cr to 6.85 mg/dL. Anuria persisted. Intravenous furosemide 100 mg was administered. Approximately 2 hours later, urine outflow was observed. 4 days after discontinuation: BUN 47.5 mg/dL, Cr 4.48 mg/dL

				5 days after discontinuation	BUN 20.6 mg/dL, Cr 1.18 mg/dL
				6 days after discontinuation	BUN 13.2 mg/dL, Cr 0.85 mg/dL Acute renal failure resolved.
				13 days after discontinuation	A renal biopsy was performed. Site name: Kidney Diagnostic results: Compatible with thrombotic microangiopathy in healing stage, kidney needle biopsy Findings: 2 renal needle biopsies, 23 glomeruli The most characteristic change was the presence of acidophilic, reddish debris-like structures by Masson staining in the capillaries of approximately half of the glomeruli. They were amorphous and unstructured, and PAS was slightly positive or negative. Most of these did not go so far as to occlude the capillaries, and the lumen was open in many cases. It is highly likely that it was a microthrombus that is dissolving. Other changes included mild and segmental mesangial cell proliferation in approximately 1/3 of glomeruli. There was little mesangium substrate proliferation. Also, there were no thickening of the basement membrane, no adhesions or crescent formation of the glomerular tuft and Bowman's capsule, and no fibrinoid necrosis of the capillary wall. Generally, the glomeruli showed mild changes except for thrombus formation. There were no changes of note in the stroma. No vasculitis or thrombus formation was observed. Although focal mesangioproliferative glomerulonephritis would be subjected to a differential diagnosis, emphasis should be placed on the thrombophilic changes.

Laboratory test value

	9 days before admin.	Day 1 of admin.	Day 41 of admin.	Day 62 of admin.	1 day after discon-tinuation	2 days after discon-tinuation	3 days after discon-tinuation	4 days after discon-tinuation	5 days after discon-tinuation	6 days after discon-tinuation	14 days after discon-tinuation
PLT ($x10^4$ /mm^3)	5.0	18.6	10.9	13.5	11.3	11.9	14.1	14.4	13.5	13.0	15.0
Hb (g/dL)	10.3	10.1	11.8	8.6	8.7	8.3	8.4	7.6	6.9	7.0	9.4
LDH (IU/L)	266	284	383	308	334	450	444	362	-	278	280
BUN (mg/dL)	14.1	9.5	19.3	12.3	18.0	28.4	42.3	47.5	20.6	13.2	14.6
Cr (mg/dL)	0.65	0.69	0.97	0.78	2.35	4.68	6.85	4.48	1.18	0.85	0.93

Concomitant drugs: Prednisolone, vincristine sulfate, sulfamethoxazole/trimethoprim, famotidine, fluconazole

3 Revision of Precautions (No.337)

This section presents details of revisions to the Precautions and brand names of drugs that have been revised in accordance with the Notifications dated October 19, November 16, 2022.

1 Vaccines
Coronavirus modified uridine RNA vaccine (SARS-CoV-2) (Comirnaty RTU intramuscular injection (Bivalent: Original/Omicron BA.1), Comirnaty RTU intramuscular injection (Bivalent: Original/Omicron BA.4-5), Spikevax Intramuscular Injection (Bivalent: Original/Omicron BA.1))

Brand name	Comirnaty RTU intramuscular injection (Pfizer Japan Inc.), Spikevax Intramuscular Injection (Moderna Japan Co., Ltd.)
[Under new instructions]	
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION	Timing of vaccination The booster dose may be administered at least 3 months after receiving the previous SARS-CoV-2 vaccine.

2 Vaccines
Coronavirus modified uridine RNA vaccine (SARS-CoV-2) (Comirnaty intramuscular injection (Monovalent: Original))

Brand name	Comirnaty intramuscular injection (Pfizer Japan Inc.)
[Under new instructions]	
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION	Individuals who receive vaccinations Individuals 12 years of age and older who have previously received SARS-CoV-2 vaccines as primary series or a booster dose/doses. The necessity of a booster dose should be judged based on the benefit/risk balance, the prevalence status of SARS-CoV-2, and the characteristics of each person. Timing of vaccination The booster dose may be administered at least 3 months after receiving the previous SARS-CoV-2 vaccine. (deleted) The effectiveness and safety on the booster dose of this vaccine in people who have received SARS-CoV-2 vaccines other than this vaccine have not been established.

3 Vaccines
Coronavirus modified uridine RNA vaccine (SARS-CoV-2) (Spikevax Intramuscular Injection (Monovalent: Original))

Brand name	Spikevax Intramuscular Injection (Moderna Japan Co., Ltd.)
[Under new instructions]	
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION	Individuals who receive vaccinations Individuals 18 years of age and older who have previously received SARS-CoV-2 vaccines as primary series or a booster dose/doses. The necessity of a booster dose should be judged based on the benefit/risk balance, the prevalence status of SARS-CoV-2, and the characteristics

	of each person. Timing of vaccination The booster dose may be administered at least 3 months after receiving the previous SARS-CoV-2 vaccine. (deleted) The effectiveness and safety on the booster dose of this vaccine in people who have received SARS-CoV-2 vaccines other than this vaccine have not been established.

4 Diuretics, antihypertensives

Hydrochlorothiazide

Brand name	Hydrochlorothiazide Tablets 12.5 mg "Towa," Tablets 25 mg "Towa," Hydrochlorothiazide OD Tablets 12.5 mg "Towa" (Towa Pharmaceutical Co., Ltd.)
[Under old instructions]	
Adverse Reactions **Clinically Significant Adverse Reactions**	Interstitial pneumonia, pulmonary oedema, acute respiratory distress syndrome: Interstitial pneumonia, pulmonary oedema may occur. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken. In addition, it has been reported that acute respiratory distress syndrome developed within minutes to hours after taking hydrochlorothiazide.
[Under new instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Interstitial pneumonia, pulmonary oedema, acute respiratory distress syndrome Interstitial pneumonia, pulmonary oedema may occur. In addition, it has been reported that acute respiratory distress syndrome developed within minutes to hours after taking hydrochlorothiazide.

5 Antihypertensives

[1] Candesartan cilexetil/hydrochlorothiazide
[2] Valsartan/hydrochlorothiazide

Brand name	[1] Ecard Combination Tablets LD, HD (Teva Takeda Yakuhin Ltd.), and the others [2] Co-Dio combination Tablets MD, EX (Novartis Pharma K.K.), and the others
[Under old instructions]	
Adverse Reactions **Clinically Significant Adverse Reactions**	Pulmonary oedema, acute respiratory distress syndrome: Pulmonary oedema may occur. Patients should be monitored carefully. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken immediately. In addition, it has been reported that acute respiratory distress syndrome developed within minutes to hours after taking hydrochlorothiazide.
[Under new instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Pulmonary oedema, acute respiratory distress syndrome Pulmonary oedema may occur. In addition, it has been reported that acute respiratory distress syndrome developed within minutes to hours after taking hydrochlorothiazide.

6 Antihypertensives

Losartan potassium/hydrochlorothiazide

Brand name	Preminent Tablets LD, HD (Organon K.K.), and the others
[Under old instructions]	

Adverse Reactions Clinically Significant Adverse Reactions	Interstitial pneumonia, pulmonary oedema, acute respiratory distress syndrome: Interstitial pneumonia, pulmonary oedema may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken immediately. In addition, it has been reported that acute respiratory distress syndrome developed within minutes to hours after taking hydrochlorothiazide.
[Under new instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Interstitial pneumonia, pulmonary oedema, acute respiratory distress syndrome Interstitial pneumonia, pulmonary oedema may occur. In addition, it has been reported that acute respiratory distress syndrome developed within minutes to hours after taking hydrochlorothiazide.

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

Roxadustat

Brand name	Evrenzo Tablets 20 mg, 50 mg, 100 mg (Astellas Pharma Inc.)
[Under new instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	Central hypothyroidism may occur during administration of this drug. Cases in which central hypothyroidism developed approximately 2 weeks after initiation of administration have been reported. Patients should be carefully monitored through methods including periodical thyroid function tests (measurement of thyroid-stimulating hormone (TSH), free T3, free T4) during treatment with this drug.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Central hypothyroidism Central hypothyroidism, in which the blood TSH level is within the normal range or low, may occur. If symptoms or signs appear, appropriate measures should be taken such as discontinuation of this drug and administration of thyroid hormone preparations as necessary.

8 Other antitumor agents

Imatinib mesilate

Brand name	Glivec Tablets 100 mg (Novartis Pharma K.K.), and the others
[Under old instructions]	
Adverse Reactions Clinically Significant Adverse Reactions (newly added)	Thrombotic microangiopathy: Thrombotic microangiopathy may occur. If anaemia accompanied by schizocytes, thrombocytopenia, renal impairment, etc. are observed, administration of this drug should be discontinued, and appropriate measures should be taken.
[Under new instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Thrombotic microangiopathy If anaemia accompanied by schizocytes, thrombocytopenia, renal impairment, etc. are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

9 Antibiotic preparations acting mainly on gram-positive and gram-negative bacteria

Amoxicillin hydrate

Brand name	Sawacillin Capsules 125, 250, Sawacillin Fine Granules 10%, Sawacillin Tablets 250 (LTL Pharma Co., Ltd), Pasetocin Capsules 125, Pasetocin Fine Granules 10% (Sandoz Pharma K.K.), and the others

[Under old instructions]

Important Precautions	No methods are currently available for predicting onset of shock, anaphylaxis, or acute coronary syndrome accompanying allergic reaction with reasonable certainty. A thorough medical interview should be conducted regarding patient's medical history of these events, etc. in advance. In addition, it should be ensured that a history of allergy to antibiotics was checked.
Adverse Reactions Clinically Significant Adverse Reactions (newly added)	Acute coronary syndrome accompanying allergic reaction: Acute coronary syndrome accompanying allergic reaction may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

[Under new instructions]

8. IMPORTANT PRECAUTIONS (newly added)	No methods are currently available for predicting onset of shock, anaphylaxis, or acute coronary syndrome accompanying allergic reaction with reasonable certainty. A thorough medical interview should be conducted regarding patient's medical history of these events, etc. in advance. In addition, it should be ensured that a history of allergy to antibiotics was checked.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Acute coronary syndrome accompanying allergic reaction

10 Antibiotic preparations acting mainly on gram-positive and gram-negative bacteria

Potassium clavulanate/amoxicillin hydrate

Brand name	Augmentin Combination Tablets 125SS, 250RS, Clavamox Combination Dry Syrup for Pediatric (GlaxoSmithKline K.K.)

[Under new instructions]

8. IMPORTANT PRECAUTIONS	No methods are currently available for predicting onset of shock, anaphylaxis, or acute coronary syndrome accompanying allergic reaction with reasonable certainty. A thorough medical interview should be conducted regarding patient's medical history of these events, etc. in advance. In addition, it should be ensured that a history of allergy to antibiotics was checked.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Acute coronary syndrome accompanying allergic reaction

11 Other antibiotic preparations

[1] Vonoprazan fumarate/amoxicillin hydrate/clarithromycin
[2] Vonoprazan fumarate/amoxicillin hydrate/metronidazole

Brand name	[1] Vonosap Pack 400, 800 (Takeda Pharmaceutical Company Limited) [2] Vonopion Pack (Takeda Pharmaceutical Company Limited)

[Under old instructions]

Important Precautions	(Amoxicillin hydrate) No methods are currently available for predicting onset of shock, anaphylaxis, or acute coronary syndrome accompanying allergic reaction with reasonable certainty. A thorough medical interview should be conducted regarding patient's medical history of these events, etc.

	in advance. In addition, it should be ensured that a history of allergy to antibiotics was checked.
Adverse Reactions Clinically Significant Adverse Reactions (newly added)	(Amoxicillin hydrate) Acute coronary syndrome accompanying allergic reaction: Acute coronary syndrome accompanying allergic reaction may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.
[Under new instructions]	
8. IMPORTANT PRECAUTIONS	<Amoxicillin hydrate> No methods are currently available for predicting onset of shock, anaphylaxis, or acute coronary syndrome accompanying allergic reaction with reasonable certainty. A thorough medical interview should be conducted regarding patient's medical history of these events, etc. in advance. In addition, it should be ensured that a history of allergy to antibiotics was checked.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	<Amoxicillin hydrate> Acute coronary syndrome accompanying allergic reaction

12 Other antibiotic preparations

Rabeprazole sodium/amoxicillin hydrate/clarithromycin

Brand name	Rabecure Pack 400, 800 (Eisai Co., Ltd.)
[Under old instructions]	
Important Precautions	(Amoxicillin hydrate) No methods are currently available for predicting onset of shock, anaphylaxis, or acute coronary syndrome accompanying allergic reaction with reasonable certainty. A thorough medical interview should be conducted regarding patient's medical history of these events, etc. in advance. In addition, it should be ensured that a history of allergy to antibiotics was checked.
Adverse Reactions Clinically Significant Adverse Reactions (newly added)	(Amoxicillin hydrate) Acute coronary syndrome accompanying allergic reaction: Acute coronary syndrome accompanying allergic reaction may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.
[Under new instructions]	
8. IMPORTANT PRECAUTIONS	<Amoxicillin hydrate> No methods are currently available for predicting onset of shock, anaphylaxis, or acute coronary syndrome accompanying allergic reaction with reasonable certainty. A thorough medical interview should be conducted regarding patient's medical history of these events, etc. in advance. In addition, it should be ensured that a history of allergy to antibiotics was checked.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	<Amoxicillin hydrate> Acute coronary syndrome accompanying allergic reaction

13 Other antibiotic preparations

Rabeprazole sodium/amoxicillin hydrate/metronidazole

Brand name	Rabefine Pack (Eisai Co., Ltd.)
[Under new instructions]	
8. IMPORTANT PRECAUTIONS	<Amoxicillin hydrate> No methods are currently available for predicting onset of shock, anaphylaxis, or acute coronary syndrome accompanying allergic reaction with reasonable certainty. A thorough medical interview should be conducted regarding patient's medical history of these events, etc. in advance. In addition, it should be ensured that a history of allergy to antibiotics was checked.
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions (newly added)	<Amoxicillin hydrate> Acute coronary syndrome accompanying allergic reaction

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 October 31, 2022)
◎: Products for which EPPV was initiated after September 1, 2022

	Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
◎	Rivaroxaban[*1] / Xarelto tablets 2.5 mg	Bayer Yakuhin Ltd.	October 24, 2022
◎	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) / Comirnaty intramuscular injection for 6 months to 4 years old	Pfizer Japan Inc.	October 19, 2022
◎	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) / COMIRNATY RTU intramuscular injection (Bivalent: Original/Omicron BA.4-5)	Pfizer Japan Inc.	October 7, 2022
	Fesoterodine fumarate[*2] / Toviaz Tablets 4 mg, 8 mg	Pfizer Japan Inc.	September 26, 2022
	Aflibercept (genetical recombination) [*3] / Eylea solution for IVT inj. 40 mg/mL	Bayer Yakuhin Ltd.	September 26, 2022
	Upadacitinib hydrate[*4] / [1] Rinvoq Tablets 7.5 mg, [2] 15 mg, [3] 30 mg, [4] 45 mg	AbbVie GK	September 26, 2022
	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2)[*5] / Spikevax Intramuscular Injection	Moderna Japan Co., Ltd.	September 20, 2022
	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2)[*6] / Comirnaty RTU intramuscular injection (Bivalent: Original/Omicron BA.1)	Pfizer Japan Inc.	September 14, 2022
	Ethyl icosapentate / Epadel EM Capsules 2 g	Mochida Pharmaceuticals Co. Ltd.	September 12, 2022
	Sutimlimab (genetical recombination) / Enjaymo for I.V. infusion 1.1 g	Sanofi K.K.	September 8, 2022
	Tixagevimab (genetical recombination) and cilgavimab (genetical recombination) / Evusheld Intramuscular Injection Set	AstraZeneca K.K.	August 31, 2022

Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
Pimitespib Jeselhy tablets 40 mg	TAIHO Pharmaceutical Co., Ltd.	August 30, 2022
Icatibant acetate Firazyr subcutaneous injection 30 mg syringes	Takeda Pharmaceutical Company Limited.	August 24, 2022
Ravulizumab (genetical recombination) [*7] Ultomiris for Intravenous Infusion 300 mg, 300 mg/3 mL, Ultomiris for Intravenous Infusion 1100 mg/11 mL	Alexion Pharma Godo Kaisha	August 24, 2022
Landiolol hydrochloride [*8] Onoact for I. V. Infusion 50 mg, 150 mg	Ono Pharmaceutical Co., Ltd.	August 24, 2022
Darinaparsin Darvias Injection 135 mg	Solasia Pharma K.K.	August 22, 2022
Vestronidase alfa (genetical recombination) Mepsevii Intravenous Infusion 10 mg	Ultragenyx Japan K.K.	August 22, 2022
Vosoritide (genetical recombination) Voxzogo for Subcutaneous Injection 0.4 mg, 0.56 mg, 1.2 mg	BioMarin Pharmaceutical Japan K.K.	August 19, 2022
Nemolizumab (genetical recombination) Mitchga 60 mg Syringes	Maruho Co., Ltd.	August 8, 2022
Freeze-dried Smallpox Vaccine Prepared in Cell Culture [*9] Freeze-dried Smallpox Vaccine Prepared in Cell Culture LC16 “KMB”	KM Biologics Co., Ltd.	August 2, 2022
[1] [2] Cabotegravir, [3] Cabotegravir sodium, [4] [5] Rilpivirine [1] Vocabria Aqueous Suspension for IM Injection 400 mg, [2] Vocabria Aqueous Suspension for IM Injection 600 mg, [3] Vocabria Tablets 30 mg, [4] Rekambys Aqueous Suspension for IM Injection 600 mg, [5] Rekambys Aqueous Suspension for IM Injection 900 mg	[1] [2] [3] ViiV Healthcare K.K. [4] [5] Janssen Pharmaceutical K.K.	June 27, 2022
Emicizumab (genetical recombination) [*10] Hemlibra for Subcutaneous Injection 30 mg, 60 mg, 90 mg, 105 mg, 150 mg	Chugai Pharmaceutical Co., Ltd.	June 20, 2022
Daptomycin Cubicin IV 350 mg	MSD K.K.	June 20, 2022
Brolucizumab (genetical recombination) [*11] Beovu kit for intravitreal injection 120 mg/mL	Novartis Pharma K.K.	June 20, 2022
Rituximab (genetical recombination) [*12] Rituxan Intravenous Infusion 100 mg, 500 mg	Zenyaku Kogyo Co., Ltd.	June 20, 2022
Lasmiditan succinate		

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
	Reyvow tablets 50 mg, 100 mg	Eli Lilly Japan K.K.	June 8, 2022
	Avacopan Tavneos Capsules 10 mg	Kissei Pharmaceutical Co., Ltd.	June 7, 2022
	Olipudase alfa (genetical recombination) Xenpozyme for I.V. Infusion 20 mg	Sanofi K.K.	June 3, 2022
	Finerenone Kerendia tablets 10 mg, 20 mg	Bayer Yakuhin Ltd.	June 2, 2022
	Valbenazine tosilate Dysval Capsules 40 mg	Mitsubishi Tanabe Pharma Corporation	June 1, 2022
	Difamilast Moizerto ointment 0.3%, 1%	Otsuka Pharmaceutical Co., Ltd.	June 1, 2022
	Carotegrast methyl Carogra Tablets 120 mg	EA Pharma Co., Ltd.	May 30, 2022
	Fosnetupitant chloride hydrochloride Arokaris I.V. infusion 235 mg	TAIHO Pharmaceutical Co., Ltd.	May 30, 2022
	Tolvaptan sodium phosphate Samtasu for I.V. infusion 8 mg, 16 mg	Otsuka Pharmaceutical Co., Ltd.	May 30, 2022
	Lanadelumab (genetical recombination) Takhzyro subcutaneous injection 300 mg syringes	Takeda Pharmaceutical Company Limited.	May 30, 2022
	Metronidazole*13 Rozex Gel 0.75%	Maruho Co., Ltd.	May 26, 2022
	Asciminib hydrochloride Scemblix tablets 20 mg, 40 mg	Novartis Pharma K.K.	May 25, 2022
	Faricimab (genetical recombination) Vabysmo solution for Intravitreal Injection 120 mg/mL	Chugai Pharmaceutical Co., Ltd.	May 25, 2022
	Andexanet alfa (genetical recombination) Ondexxya for Intravenous Injection 200 mg	Alexion Pharma Godo Kaisha	May 25, 2022
	Glycopyrronium tosilate hydrate Rapifort Wipes 2.5%	Maruho Co., Ltd.	May 23, 2022
	Recombinant COVID-19 (SARS-CoV-2) vaccine Nuvaxovid Intramuscular Injection	Takeda Pharmaceutical Company Limited.	May 10, 2022
	Efgartigimod Alfa (genetical recombination) Vyvgart for Intravenous Infusion 400 mg	argenx Japan K.K.	May 9, 2022

*1 Prevention of thrombus/embolus formation in patients with peripheral arterial disease after lower extremity revascularization

*2 A drug with a new additional pediatric dosage indicated for urinary management in patients with neurogenic bladder

*3 Retinopathy of prematurity

*4 [1] [2] [3] Remission induction and maintenance therapy for moderate to severe ulcerative colitis (only for patients who have not adequately responded to conventional treatments), [4] remission induction therapy for moderate to severe ulcerative colitis (only for patients who have not adequately responded to conventional treatments)

*5 Prevention of infectious disease caused by SARS-CoV-2

*6 Prevention of infectious disease caused by SARS-CoV-2

*7 Treatment of generalized myasthenia gravis (only for patients whose symptoms are difficult to control with high-dose intravenous immunoglobulin therapy or plasmapheresis)

*8 A drug with a new additional pediatric dosage indicated for the treatment of tachyarrhythmia (supraventricular

tachycardia, atrial fibrillation and atrial flutter) in patients with low cardiac function

*9 Monkeypox

*10 Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with acquired hemophilia A

*11 Diabetic macular oedema

*12 Prevention of recurrence of neuromyelitis optica spectrum disorder (including neuromyelitis optica)

*13 Rosacea