# Pharmaceuticals and Medical Devices Safety Information

# No. 393

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Available information is listed here

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# Pharmaceuticals and Medical Devices Safety Information

## No. 393

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

| | |
|---|---|
| ADR | Adverse drug reaction |
| EPPV | Early Post-marketing Phase Vigilance |
| FY | Fiscal Year |
| MAH | Marketing authorization holder |
| MHLW | Ministry of Health, Labour and Welfare |
| PMDA | Pharmaceuticals and Medical Devices Agency |

# 1
# The Manuals for Management of Various Serious Adverse Drug Reactions

## 1. Introduction

Conventional safety measures implemented in Japan had been drug-oriented and mainly “alert-issue” and “post-event response” types, i.e., information of adverse drug reactions (ADRs) was collected and evaluated for each drug and notified to the clinical settings. However, these types of measures may not be, occasionally, effective enough for early detection of adverse drug reactions, leading to serious conditions, for example, for the following reasons:

(1) Adverse drug reactions may occur in the organs in which physicians are not specialized.
(2) The incidence of serious adverse drug reactions is generally low, and some physicians may have little experience with such events.

Therefore, the Ministry of Health, Labour and Welfare (MHLW) has implemented the “Project of Comprehensive Measures for Serious Adverse Drug Reactions” (Hereinafter referred to as the "Project," the Project has been ongoing as the “Development Project of the Manuals for Management of Various Serious Adverse Drug Reactions” since FY 2021.) since 2005 in order to develop safety measures that “predict” and “prevent” adverse drug reactions by preparing adverse reaction-oriented safety measures, in addition to conventional drug-oriented adverse drug reaction safety measures, and to promote research to elucidate the mechanism of adverse drug reactions, etc.

In this project, “The Manuals for Management of Various Serious Adverse Drug Reactions” (hereinafter referred to as "the Manuals") were compiled from FY 2005 to FY 2010 by the Committee on the Comprehensive Actions for Serious Adverse Drug Reactions who reviewed and compiled the drafts prepared by manual preparation committees organized in related academic societies through discussion with the Japanese Society of Hospital Pharmacists (JSHP) as entrusted by the MHLW in this project. The drafts were prepared with reference to academic papers, various guidelines, health and labour science research project reports, PMDA health and welfare service reports, etc.

In order to promote further utilization of the Manuals after a certain period of time has elapsed since its compilation, revisions based on the latest knowledge have been made over the five years since FY 2016, with the cooperation of related academic societies and others. In addition, we continue to revise the Manuals and prepare new ones as necessary, and promote them to the general public.

## 2. Progress of revisions, etc.

In FY 2020, we completed the revisions of the following manuals, etc. The revisions were reported and discussed at the meeting of the Committee on the Comprehensive Actions for Serious Adverse Drug Reactions held on October 15, 2021 and were published in February 2022.

| Author | Manual title | Category* |
|---|---|---|
| The Japanese Society of Hematology | Immune-related adverse events of immune checkpoint inhibitors | New |
| | Bleeding tendency | Revision |
| | Agranulocytosis (granulocytopenia, neutropenia) | Revision |
| | Thrombocytopenia | Revision |
| | Thrombotic thrombocytopenic purpura (TTP) | Revision |
| | Heparin-induced thrombocytopenia (HIT) | Revision |

| | | |
|---|---|---|
| Japanese Society of Neurology | Drug-induced parkinsonism | Revision |
| | Dyskinesia | Revision |
| | Rhabdomyolysis | Simple update |
| | Leukoencephalopathy | Simple update |
| | Peripheral neuropathy | Simple update |
| | Guillain-Barré syndrome | Simple update |
| | Convulsions/epilepsy | Simple update |
| | Ataxia | Simple update |
| | Headache | Simple update |
| | Aseptic meningitis | Simple update |
| | Acute disseminated encephalomyelitis | Simple update |
| The Japanese Respiratory Society | NSAIDs-exacerbated respiratory disease (aspirin-induced asthma, antipyretic-analgesics-induced asthma, aspirin-intolerant asthma, NSAIDs-induced asthma) | Revision |
| | Acute respiratory distress syndrome/pulmonary oedema † The 2 manuals for acute lung injury/acute respiratory distress syndrome and pulmonary edema integrated | Revision |
| | Pleuritis, pleural effusion | Revision |
| | Drug-induced eosinophilic pneumonia | Revision |
| | Alveolar hemorrhage (pulmonary hemorrhage, diffuse alveolar hemorrhage) | Revision |
| Japanese Society of Otorhinolaryngology-Head and Neck Surgery | Drug-induced hearing loss (caused by aminoglycoside antibiotics, platinum preparations, salicylic acid, loop diuretics) | Revision |
| The Japanese Stomatological Society | Drug-induced taste disturbance | Revision |
| The Japan Endocrine Society | Pseudoaldosteronism | Revision |
| | Thyrotoxicosis | Revision |
| | Hypothyroidism | Revision |
| The Japanese Society of Clinical Neuropsychopharmacology | Lithium toxicity | New |
| | Medication-induced or withdrawal delirium | New |
| | Benzodiazepine dependence | New |
| | Neuroleptic malignant syndrome | Simple update |
| | Drug-induced depression | Simple update |
| The Japanese Dermatological Association | Drug-induced hypersensitivity syndrome | Simple update |
| | Acute generalised exanthematous pustulosis | Simple update |
| | Medicament contact dermatitis | Simple update |
| Japanese Society of Oral and Maxillofacial Surgeons | Stomatitis medicamentosa | Simple update |
| | Chemotherapy-induced oral mucositis (stomatitis) | Simple update |

*Manuals that were categorized as simple updates were revised for reference materials only.

The Manuals published this time, following the manuals published last year, include explanations about relief for sufferers of ADRs at the end of the section “About this manual” in the beginning of each manual. The manuals also provide the number of payments for relief benefits in

the past 5 years under the Relief System for Adverse Drug Reactions and information concerning the Relief System for Adverse Drug Reactions at the end of each manual.

## 3. Plans for further revisions, etc.

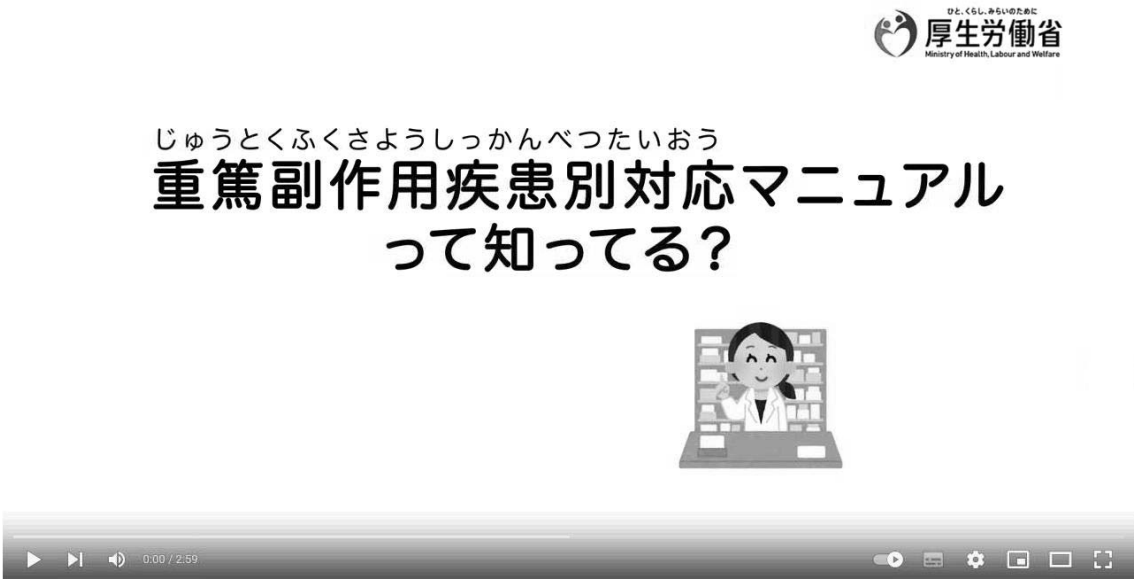
In FY 2021, the following Manuals were revised and prepared based on the opinions of the Committee and the academic societies. The Manuals are scheduled to be published after being reported and discussed at the Committee on the Comprehensive Actions for Serious Adverse Drug Reactions.

| Author | Manual title | Category |
|---|---|---|
| The Japanese Dermatological Association | Medicament contact dermatitis | Revision |
| Japanese Society of Oral and Maxillofacial Surgeons | Stomatitis medicamentosa | Revision |
| | Chemotherapy-induced oral mucositis (stomatitis) | Revision |
| Japanese Ophthalmological Society | Retina and optic pathway disorders<br>† Items will be added for retinal detachment | Revision |
| Japanese Society of Neurology | Progressive multifocal leukoencephalopathy (PML) | New |

## 4. Increasing awareness of the Manuals

In order to further disseminate the Manuals and to promote early detection and treatment of serious adverse drug reactions, we have been working on awareness-raising initiatives of the Manuals since FY 2021.

In May 2022, we prepared and published an educational video about the Manuals. The video explains how to use the Manuals in easy-to-understand language for patients, intending to be used in waiting rooms of clinics, hospitals, and pharmacies. Please download it from the following URL.
(https://www.pmda.go.jp/safety/info-services/drugs/adr-info/manuals-for-public/0003.html (only in Japanese))



## 5. Closing remark

Healthcare professionals are requested to continue to cooperate in the proper use of drugs by utilizing the Manuals and informing patients of them as necessary. The Manuals are available on the MHLW and PMDA websites.

[References]
Previous articles introducing the Initiative of Revision of the Manuals for Management of Various Serious Adverse Drug Reactions

1. Pharmaceuticals and Medical Devices Safety Information No.348 (https://www.pmda.go.jp/files/000221054.pdf)
2. Pharmaceuticals and Medical Devices Safety Information No.357 (https://www.pmda.go.jp/files/000226311.pdf)
3. Pharmaceuticals and Medical Devices Safety Information No.368 (https://www.pmda.go.jp/files/000232763.pdf)

MHLW website “Manuals for Management of Various Serious ADRs” (https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/topics/tp061122-1.html) (only in Japanese)

PMDA website “Manuals for Management of Various Serious ADRs” (https://www.pmda.go.jp/safety/info-services/drugs/adr-info/manuals-for-hc-pro/0001.html) (only in Japanese)

# 2

# Important Safety Information

Regarding the revision of the Precautions of drugs in accordance with the Notification dated June 14, 2022, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

## 1 Cetuximab sarotalocan sodium (genetical recombination)

| | |
|---|---|
| **Brand name (name of company)** | Akalux IV Infusion 250 mg (Rakuten Medical K.K.) |
| **Therapeutic category** | Other antitumor agents |
| **Indications** | Unresectable, locally advanced or recurrent head and neck cancer |

**PRECAUTIONS (revised language is underlined)**

**[Under new instructions]**

| | |
|---|---|
| **8. IMPORTANT PRECAUTIONS (newly added)** | Fistula, mucocutaneous ulceration or necrosis may occur at the site of laser irradiation. Whether a tumour invasion into the skin or mucous membrane has occurred should be adequately confirmed prior to the administration of this drug. In addition, during the treatment with this drug, the patient's condition including the presence or absence of fistula, ulceration or necrosis should be adequately monitored. |
| **9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS**<br>**9.1 Patients with complication or history of diseases, etc. (newly added)** | Patients with tumour invasion into the skin or mucous membrane<br>In patients with tumour invasion into the skin or mucous membrane, the effectiveness and risks of this drug should be carefully considered prior to deciding whether or not to treat with this drug. Fistula, mucocutaneous ulceration or necrosis may occur at the site of laser irradiation. |
| **11. ADVERSE REACTIONS**<br>**11.1 Clinically Significant Adverse Reactions (newly added)** | Fistula, mucocutaneous ulceration or necrosis<br>Fistula, skin ulceration, mucosal ulceration, skin necrosis, or mucosal necrosis may occur at the site of laser irradiation. |
| **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<br>Cases involving anaphylaxis: 4 (No patient mortalities)<br>Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 41<br>Japanese market launch: January 2021 |

| No. | Patient | | Daily dose/ administration duration | Adverse reaction |
|---|---|---|---|---|
| | Sex/ age | Reason for use (complication) | | Clinical course and treatment |
| 1 | Male 70s | Head and neck cancer (none) | 640 mg/m$^2$ (1 day per 1 cycle, 3 cycles) | **Fistula**<br>Primary disease: Unresectable, locally recurrent head and neck cancer<br>(Primary lesion location: Lips/mouth<br>Histopathological type of the primary lesion: Squamous cell carcinoma<br>Tumor location: Buccal mucosa of the right cheek<br>ECOG PS: 0<br>TNM classification: T3N0M0<br>Stage: III)<br>Medical history: Hypopharyngeal cancer, gingival cancer of the upper jaw<br>Prior treatments: Tumour excision of the buccal mucosa, boron-neutron capture therapy (BNCT)<br>Before administration: The risk of developing fistula was explained to the patient, and informed consent was obtained.<br>Day 1 of administration (the 1st cycle): Cetuximab sarotalocan sodium 640 mg/m$^2$ was administered (the 1st cycle). Grade 1 back pain developed, lasting for approximately 2 minutes, and was resolved.<br>1 day after administration: Laser light irradiation of the 1st cycle was performed. The tumor site of the buccal mucosa of the right cheek was punctured by four needle catheters orally, and it was punctured by one catheter percutaneously through the right mandibular region. Cylindrical diffuser was used for irradiation. Grade 2 increased blood pressure developed. Administration of antihypertensive drugs was initiated. (The blood pressure returned to normal the next day.) After the procedure was completed and the patient awoke, Grade 2 pain (right buccal region) developed (resolving after 3 days). Grade 2 oedema (head and neck) developed (resolved after 5 days).<br>21 days after administration: Grade 2 small fistula developed in the right buccal region, the irradiation site. The fistula area was only protected by gauze.<br>28 days after administration (the 2nd cycle): Cetuximab sarotalocan sodium 640 mg/m$^2$ was administered (the 2nd cycle). Grade 1 back pain developed (resolved the next day).<br>29 days after administration: Laser light irradiation of the 2nd cycle was performed. As with the first treatment, the tumor site of the buccal mucosa of the right cheek was punctured by two needle catheters orally, and a cylindrical diffuser was used for irradiation. During laser irradiation, Grade 2 pain (right buccal region) developed (resolving after 3 days). After the irradiation, debridement was conducted for necrotic tissue.<br>30 days after administration: Grade 2 face oedema developed (resolved after 3 days).<br>63 days after administration (the 3rd cycle): Cetuximab sarotalocan sodium 640 mg/m$^2$ was administered (the 3rd cycle). Approximately 5 minutes after |

| | |
|---|---|
| (Day of termination) | administration of cetuximab sarotalocan sodium, Grade 2 back pain developed, lasting for approximately 5 minutes, and was resolved. |
| 1 day after termination | Laser light irradiation of the 3rd cycle was performed.<br>The buccal mucosa of the right cheek was punctured by two needle catheters orally, and it was punctured by three catheters percutaneously through the right mandibular area. A cylindrical diffuser was used for irradiation. Grade 2 pain (right buccal region) developed (resolving after 3 days). |
| 2 days after termination | Grade 2 face oedema developed (resolved after 3 days). |
| 29 days after termination | Fistula in the buccal mucosa of the right cheek enlarged. |
| 43 days after termination | Treatment was shifted to drug treatment (fluorouracil + cisplatin + pembrolizumab) due to disease progression.<br>The fistula area was only protected by gauze. |
| 56 days after termination | Drug treatment (fluorouracil + cisplatin + pembrolizumab) was initiated for the treatment of the primary disease. Fistula was not resolved. |
| 98 days after termination | Administration of fluorouracil + cisplatin + pembrolizumab was completed. |

**Laboratory test value**

| | Date unknown | 1 day after administration |
|---|---|---|
| Diastolic blood pressure | — | 73 |
| Systolic blood pressure | — | 124 (before laser light irradiation)<br>170 (during treatment by laser light irradiation) |
| Heart rate | 74 | 79 |

Concomitant drugs: Chlorpheniramine maleate, dexamethasone sodium phosphate

## 2 Nirmatrelvir/ritonavir

| | |
|---|---|
| **Brand name (name of company)** | Paxlovid Pack (Pfizer Japan Inc.) |
| **Therapeutic category** | Anti-virus agents |
| **Indications** | Treatment of disease caused by SARS-CoV-2 infection (COVID-19) |

**PRECAUTIONS (revised language is underlined)**

**[Under new instructions]**

| | |
|---|---|
| **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 event is reasonably possible) reported during the previous approximately 3-year period<br>Cases involving anaphylaxis: 1 (No patient mortalities)<br>Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 5 940*<br>*Number of patients who had been administered nirmatrelvir/ritonavir during the period from February 10, 2022 to April 30, 2022<br>Japanese market launch: February 2022 |

**Case summary**

| No. | Patient | | Daily dose/ administration duration | Adverse reaction | |
|---|---|---|---|---|---|
| | Sex/ age | Reason for use (complication) | | Clinical course and treatment | |
| 1 | Male 60s | Treatment of COVID-19 (hypertension) | Nirmatrelvir 300 mg/ritonavir 100 mg, 4 days ↓ discontinued | **Anaphylactic shock** | |
| | | | | Day 1 of administration | Administration of nirmatrelvir/ ritonavir was initiated. |
| | | | | 2 days after administration | The patient's fever went down. He was unable to eat. |
| | | | | 4 days after administration | Urticaria developed. |
| | | | | 5 days after administration (Day of discontinuation) | Skin eruptions like urticaria were observed in the lower back. However, eruptions in other parts disappeared. Dizziness and malaise were observed. Glycyrrhizin/glycine/cysteine, d-chlorpheniramine maleate, Ringer's solution, adrenaline were administered, and the patient was transferred to another hospital. |
| | | | | 9 days after discontinuation | Urticaria partially remained. |
| | | | | 10 days after discontinuation | The patient was discharged from the hospital. |

**Laboratory test value**

| | Day 1 of administration | 2 days after administration | 4 days after administration | Day of discontinuation | 9 days after discontinuation | 10 days after discontinuation |
|---|---|---|---|---|---|---|
| Pulse (/min) | - | - | - | 81 | - | - |
| Body temperature (°C) | - | - | - | 36.5 | - | - |
| Blood pressure (mmHg) | - | - | - | 117/59 | - | - |
| RBC (x $10^4$/μl) | - | - | - | 4.67 | - | - |
| CRP (mg/dl) | - | - | - | 4.31 | - | - |
| WBC (x $10^4$/μl) | - | - | - | 7.7 | - | - |
| PLT (%) | - | - | - | 15.6 | - | - |
| AST (IU/L) | - | - | - | 18 | - | - |
| ALT (IU/L) | - | - | - | 18 | - | - |
| Total bilirubin (mg/dl) | - | - | - | 0.5 | - | - |
| γ-GPT (IU/L) | - | - | - | 32 | - | - |
| AL-P (IU/L) | - | - | - | 56 | - | - |
| Albumin (g/dl) | - | - | - | 3.2 | - | - |
| Creatinine (mg/dl) | - | - | - | 1.51 | - | - |
| eGFR (mL/min) | - | - | - | 37 | - | - |

Suspected concomitant drugs: Amlodipine besilate
Concomitant drugs: Metoprolol tartrate, lisinopril hydrate, doxazosin mesilate

## 3 Molnupiravir

| | |
|---|---|
| **Brand name (name of company)** | Lagevrio Capsules 200 mg (MSD K.K.) |
| **Therapeutic category** | Anti-virus agents |
| **Indications** | Treatment of disease caused by SARS-CoV-2 infection (COVID-19) |

**PRECAUTIONS (revised language is underlined)**

**[Under new instructions]**

**11. ADVERSE REACTIONS (newly added)**

11.1 Clinically Significant Adverse Reactions

Anaphylaxis

**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

Cases involving anaphylaxis: 2 (No patient mortalities)

Number of patients using the drug as estimated by the MAH during the 1-year period:

Approximately 166 000*2

*1 From December 24, 2021, the date of market launch, to April 28, 2022

*2 The number was calculated based on the prescription data reported to the Lagevrio registration center by medical institutions or dispensing pharmacies from December 24, 2021 to April 28, 2022.

Japanese market launch: December 2021

**Case summary**

| No. | Patient | | Daily dose/ administration duration | Adverse reaction |
|---|---|---|---|---|
| | Sex/ age | Reason for use (complication) | | Clinical course and treatment |
| 1 | Female 80s | Treatment of COVID-19 (chronic obstructive pulmonary disease, hypertension, hyperlipidaemia, chronic cardiac failure, cardiac valve disease, arrhythmia, chronic kidney disease, liver disorder, deafness, insomnia) | 800 mg 1 day | **Anaphylaxis**<br>3 days before administration: The patient had a history of allergy to vaccines. (Details are unknown because of difficulty interviewing due to her old age and deafness.) She had no other history of allergies than to vaccines. She had not been vaccinated with COVID-19 vaccines. COVID-19 developed, with cough and fever. Symptoms were mild, without signs of pneumonia. The result of COVID-19 testing was positive, and the patient was treated at home.<br>1 day before administration: The patient visited the hospital and was hospitalized.<br>Concomitant drugs from the day before onset of anaphylaxis to immediately before the onset:<br>Azilsartan, diltiazem hydrochloride, amlodipine besilate, tiotropium bromide hydrate, and lubiprostone were administered in the morning, cilostazol in the morning and the evening, and rosuvastatin calcium in the evening. Sotrovimab (genetical recombination) 500 mg once/day at night was newly administered. Suvorexant 15 mg once /day and ramelteon 8 mg once/day before sleep were newly administered for insomnia.<br>Pulse rate (PR): Between 90 and 99 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | Day 1 of administration (day of onset, day of discontinuation) | Blood pressure (BP) before the administration of molnupiravir was 112/64 mmHg.<br>The patient took antihypertensive drugs regularly while she was hospitalized, but compliance of the drugs before hospitalization was unknown. Molnupiravir was administrated. Cilostazol and rosuvastatin calcium were supposed to be taken at the same time, according to the prescription.<br>30 minutes after administration of Molnupiravir<br>Blood pressure decreased (systolic blood pressure in the 60 mmHg range), anaphylaxis (disturbed consciousness and decreased blood pressure) developed.<br>Symptoms other than decreased blood pressure and depressed level of consciousness, such as dermatological symptoms, were not observed.<br>PR: Between 90 and 99<br>No other symptoms were noted (unclear due to mild disturbed consciousness).<br>There was faecal loading in the sigmoidal colon in the image (unknown when the image was taken), and multiple fluid-fluid levels and bowel distention on the mouth side were noted. The patient was diagnosed with subileus and was placed on fasting.<br>1 hour and 30 minutes after administration<br>BP: 69/34 mmHg<br>Lactate Ringer solution was administered at 100 mL/h.<br>Consciousness level: E3V5M6<br>$SpO_2$: 88-93% (room air)<br>$O_2$: Started at 2 L/min (nasal)<br>3 hours and 30 minutes after administration<br>BP: 75/42 mmHg<br>The dose of lactate Ringer solution was increased to 200 mL/h.<br>5 hours and 50 minutes after administration<br>Systolic blood pressure: In the 70-80 mmHg range<br>The dose of lactate Ringer solution was decreased to 80 mL/h. The consciousness level was clear.<br>6 hours and 30 minutes after administration<br>BP: 100/42 mmHg<br>9 hours and 40 minutes after administration<br>BP: 85/46 mmHg<br>14 hours after administration<br>Systolic blood pressure: In the 120 mmHg range<br>The consciousness level was clear.<br>Anaphylaxis was resolved.<br>2 days after discontinuation<br>Since a large amount of defecation was observed and no obvious abdominal symptoms were noted, fasting was lifted. (The patient was placed on fasting only on the next day of discontinuation.) The patient recovered from subileus. |
| | Laboratory test value: - | | | | |
| | Suspected concomitant drugs: Suvorexant, ramelteon, sotrovimab (genetical recombination)<br>Concomitant drugs: Azilsartan, diltiazem hydrochloride, amlodipine besilate, cilostazol, rosuvastatin calcium, tiotropium bromide hydrate, lubiprostone | | | | |

# 3
# Revision of Precautions (No.333)

This section presents details of revisions to the Precautions and brand names of drugs that have been revised in accordance with the Notifications dated June 10, June 14, 2022.

## 1 Vaccines
## Coronavirus modified uridine RNA vaccine (SARS-CoV-2) (Comirnaty intramuscular injection, Comirnaty intramuscular injection for 5 to 11 years old, Spikevax Intramuscular Injection)

| | |
|---|---|
| **Brand name** | Comirnaty intramuscular injection (Pfizer Japan Inc.), Comirnaty intramuscular injection for 5 to 11 years old (Pfizer Japan Inc.), Spikevax Intramuscular Injection (Takeda Pharmaceutical Company Limited.) |
| **[Under New instructions]** | |
| **8. IMPORTANT PRECAUTIONS (newly added)** | Cases of Guillain-Barré syndrome have been reported following inoculation with Coronavirus modified uridine RNA vaccine (SARS-CoV-2). Vaccine recipients or their caregivers should be instructed in advance to seek medical attention immediately if the vaccine recipients experience any symptoms that could suggest Guillain-Barré syndrome (such as flaccid paralysis starting from distal limb, decreased or absent tendon reflex). |

## 2 Other antitumor agents
## Cetuximab sarotalocan sodium (genetical recombination)

| | |
|---|---|
| **Brand name** | Akalux IV Infusion 250 mg (Rakuten Medical K.K.) |
| **[Under New instructions]** | |
| **8. IMPORTANT PRECAUTIONS (newly added)** | Fistula, mucocutaneous ulceration or necrosis may occur at the site of laser irradiation. Whether a tumour invasion into the skin or mucous membrane has occurred should be adequately confirmed prior to the administration of this drug. In addition, during the treatment with this drug, the patient's condition including the presence or absence of fistula, ulceration or necrosis should be adequately monitored. |
| **9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.1 Patients with complication or history of diseases, etc. (newly added)** | Patients with tumour invasion into the skin or mucous membrane<br>In patients with tumour invasion into the skin or mucous membrane, the effectiveness and risks of this drug should be carefully considered prior to deciding whether or not to treat with this drug. Fistula, mucocutaneous ulceration or necrosis may occur at the site of laser irradiation. |
| **11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)** | Fistula, mucocutaneous ulceration or necrosis<br>Fistula, skin ulceration, mucosal ulceration, skin necrosis, or mucosal necrosis may occur at the site of laser irradiation. |

## 3 Other antitumor agents
## [1] Nivolumab (genetical recombination)
## [2] Pembrolizumab (genetical recombination)

| | |
|---|---|
| **Brand name** | [1] Opdivo I.V. Infusion 20 mg, 100 mg, 120 mg, 240 mg (Ono Pharmaceutical Co., Ltd.)<br>[2] Keytruda Injection 100 mg (MSD K.K.) |
| **[Under New instructions]** | |
| **11. ADVERSE REACTIONS**<br>**11.1 Clinically Significant Adverse Reactions**<br>**(newly added)** | Severe gastritis<br>Severe gastritis considered to be caused by an immune reaction may occur. If any abnormalities are observed, appropriate measures such as administration of corticosteroids should be taken. |

4 Other antibiotic preparations

## [1] Vonoprazan fumarate/amoxicillin hydrate/metronidazole
## [2] Rabeprazole sodium/amoxicillin hydrate/metronidazole

| | |
|---|---|
| **Brand name** | [1] Vonopion Pack (Takeda Pharmaceutical Company Limited)<br>[2] Rabefine Pack (Eisai Co., Ltd.) |
| **[Under Old instructions]** | |
| **Adverse Reactions**<br>**<metronidazole>**<br>**Clinically Significant Adverse Reactions**<br>**(newly added)** | Prolonged QT, ventricular tachycardia (including torsade de pointes):<br>Prolonged QT, ventricular tachycardia (including torsade de pointes) may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken. |
| **[Under New instructions]** | |
| **11. ADVERSE REACTIONS**<br>**11.1 Clinically Significant Adverse Reactions**<br>**(newly added)** | Prolonged QT, ventricular tachycardia (including torsade de pointes) |

5 Anti-virus agents

## Nirmatrelvir/ritonavir

| | |
|---|---|
| **Brand name** | Paxlovid Pack (Pfizer Japan Inc.) |
| **[Under New instructions]** | |
| **11. ADVERSE REACTIONS**<br>**11.1 Clinically Significant Adverse Reactions**<br>**(newly added)** | Anaphylaxis |

6 Anti-virus agents

## Molnupiravir

| | |
|---|---|
| **Brand name** | Lagevrio Capsules 200 mg (MSD K.K.) |
| **[Under New instructions]** | |
| **11. ADVERSE REACTIONS**<br>**(newly added)** | 11.1 Clinically Significant Adverse Reactions<br>Anaphylaxis |

7 Antiprotozoan agents

## Metronidazole (oral dosage form)

| | |
|---|---|
| **Brand name** | Flagyl Oral Tablets 250 mg (Shionogi Pharma Co., Ltd.) |
| **[Under New instructions]** | |
| **11. ADVERSE REACTIONS** | Prolonged QT, ventricular tachycardia (including torsade de pointes) |

| | |
|---|---|
| **11.1 Clinically Significant Adverse Reactions <Common to all indications> (newly added)** | |

8 Antiprotozoan agents

## Metronidazole (injections)

| | |
|---|---|
| **Brand name** | Anaemetro Intravenous infusion 500 mg (Pfizer Japan Inc.) |
| **[Under New instructions]** | |
| **11. ADVERSE REACTIONS** | |
| **11.1 Clinically Significant Adverse Reactions (newly added)** | <u>Prolonged QT, ventricular tachycardia (including torsade de pointes)</u> |

# 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 31 May 2022)
◎: Products for which EPPV was initiated after May 1, 2022

| | Nonproprietary name / Brand name | Name of the MAH | Date of EPPV initiate |
|---|---|---|---|
| ◎ | 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[*1] / 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 |
| | Somatrogon (genetical recombination) / Ngenla Inj. 24 mg Pens, 60 mg Pens | Pfizer Japan Inc. | April 27, 2022 |
| | Gefapixant citrate / Lyfnua Tablets 45 mg | MSD K.K. | April 21, 2022 |
| | Sotorasib | Amgen K.K. | April 20, |

| Nonproprietary name<br>Brand name | Name of the MAH | Date of EPPV initiate |
|---|---|---|
| Lumakras Tablets 120 mg | | 2022 |
| Clazosentan sodium<br>Pivlaz I.V. Infusion liquid 150 mg | Idorsia Pharmaceuticals Japan Ltd. | April 20, 2022 |
| Bimekizumab (genetical recombination)<br>Bimzelx Syringe for S.C injection 160 mg, Bimzelx Autoinjector for S.C injection 160 mg | UCB Japan Co. Ltd. | April 20, 2022 |
| Filgotinib maleate*2<br>Jyseleca Tablets 100 mg, 200 mg | Gilead Sciences K.K. | March 28, 2022 |
| Selpercatinib*3<br>Retevmo Capsules 40 mg, 80 mg | Eli Lilly Japan K.K. | February 25, 2022 |
| Pegfilgrastim (genetical recombination)*4<br>G-Lasta Subcutaneous Injection 3.6 mg | Kyowa Kirin Co., Ltd. | February 25, 2022 |
| Coronavirus modified uridine RNA vaccine (SARS-CoV-2)<br>Comirnaty intramuscular injection for 5 to 11 years old | Pfizer Japan Inc. | February 22, 2022 |
| Nirmatrelvir/ritonavir<br>Paxlovid Pack | Pfizer Japan Inc. | February 14, 2022 |
| Tocilizumab (genetical recombination) *5<br>Actemra for Intravenous Infusion 80 mg, 200 mg, 400 mg | Chugai Pharmaceutical Co., Ltd. | January 21, 2022 |
| 3-Iodobenzylguanidine ($^{131}$I)<br>Raiatt MIBG-I 131 Injection | FUJIFILM Toyama Chemical Co., Ltd. | January 18, 2022 |
| Molnupiravir<br>Lagevrio Capsules 200 mg | MSD K.K. | December 24, 2021 |
| Prasugrel hydrochloride*6<br>Efient Tablets 2.5 mg, 3.75 mg | Daiichi Sankyo Co., Ltd. | December 24, 2021 |
| Azilsartan<br>Azilva Granules 1%, Azilva Tablets 10 mg, 20 mg, 40 mg | Takeda Pharmaceutical Company Limited. | December 16, 2021 |
| Abrocitinib<br>Cibinqo Tablets 50 mg, 100 mg, 200 mg | Pfizer Japan Inc. | December 13, 2021 |
| Selpercatinib<br>Retevmo Capsules 40 mg, 80 mg | Eli Lilly Japan K.K. | December 13, 2021 |
| Somapacitan (genetical recombination)<br>Sogroya Subcutaneous Injection 5 mg, 10 mg | Novo Nordisk Pharma Ltd. | December 10, 2021 |

*1 Rosacea

*2 Treatment and maintenance therapy for moderately to severely active ulcerative colitis (limited to patients who have had an inadequate response with, lost response to, or were intolerant to conventional therapies)

*3 Radically unresectable RET fusion-positive thyroid cancer, radically unresectable RET-mutant medullary thyroid cancer

*4 Mobilization of haematopoietic stem cells into peripheral blood for allogeneic blood stem cell transplantation

*5 SARS-CoV-2 pneumonia (limited to patients requiring oxygen intervention)

*6 Prevention of recurrence of ischaemic cerebrovascular disease following the former appearance of ischaemic cerebrovascular disease (associated with large-artery atherosclerosis or small-vessel occlusion) (restricted to cases with a high risk of ischaemic stroke).