Pharmaceuticals and Medical Devices Safety Information

No. 369 January 2020

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Available information is listed here

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No. 369 January 2020

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

[Outline of Information]

E: Distribution of Dear Healthcare Professional Letters of Emergency Communication R: Distribution of Dear Healthcare Professional Letters of Rapid Communications P: Revision of Precautions C: Case Summaries

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

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

Abbreviations

ADEM	Acute Disseminated Encephalomyelitis
ADR	Adverse Drug Reaction
AGEP	Acute Generalised Exanthematous Pustulosis
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
PMD Act	Act on Securing Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices
PSD	Pharmaceutical Safety Division
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
SOC	System Organ Class
PV Law	Preventative Vaccination Law

1

Safety of Influenza Antiviral Drugs

1. Introduction

As a result of deliberations at the 9th meeting of the Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council for Fiscal Year (FY) 2019 held on October 29, 2019, it was concluded that continuation of the ongoing cautionary measures pertaining to the occurrence of abnormal behavior following administration of oseltamivir phosphate (Tamiflu, etc.), zanamivir hydrate (Relenza), peramivir hydrate (Rapiacta), and laninamivir octanoate hydrate (Inavir), and baloxavir marboxil (Xofluza) (hereinafter collectively referred to as “influenza antiviral drugs”) in patients infected with influenza was appropriate based on the assessment of available evidence including newly gathered information, regardless of whether influenza antiviral drugs are administered or the specific type of drug prescribed. Based on this opinion, the Ministry of Health, Labour and Welfare (MHLW) issued a notification entitled, Efforts to Raise Awareness of the Precautions for Anti-Influenza Drugs (PSEHB/PSD Notifications No. 1121-1 by the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated November 21, 2019) to marketing authorization holders (MAHs) so that they will encourage healthcare providers to exercise further caution.

This section will provide an overview of the study results on abnormal behavior in influenza-like-illness patients and adverse reactions associated with the use of influenza antiviral drugs reported during the 2018/2019 season (September 1, 2018 to August 31, 2019) presented at the aforementioned meeting.

2. Reports of Abnormal Behavior

(1) Research on abnormal behavior associated with influenza infection

Study results for the Nationwide Investigation of the State of Instances of Abnormal Behavior in Influenza-like-Illness Patients commissioned in FY 2019 (Chief Researcher: Dr. Nobuhiko Okabe, Director General of Kawasaki City Health Safety Research Center) for the 2018/2019 season were reported. Based on these results, it was confirmed that the state of occurrences of severe abnormal behavior was relatively similar to the situation described in previous reports. The state of instances of abnormal behavior coincided with the state of instances of influenza infection as indicated in Figure 1-1. The number of days from onset of fever to emergence of abnormal behavior is as in Figure 1-2. Abnormal behavior was highly frequent to start within 2 days of fever onset. The association between abnormal behavior and administration of influenza antiviral drugs was reported as abnormal behavior occurring regardless of whether influenza antiviral drugs were administered or the specific type of drug prescribed as in Figure 1-3. Behavior such as jumping from a height and other issues that could lead to grave consequences were noted in the report. Consequently, it was agreed that ongoing cautionary measures pertaining to the occurrence of abnormal behavior in patients infected with influenza should be maintained regardless whether influenza antiviral drugs are prescribed in order to prevent grave outcomes triggered by abnormal behavior.

* Please refer to the following URL (MHLW website) for further details on the results of the study.
https://www.mhlw.go.jp/content/11120000/000560950.pdf (only in Japanese)

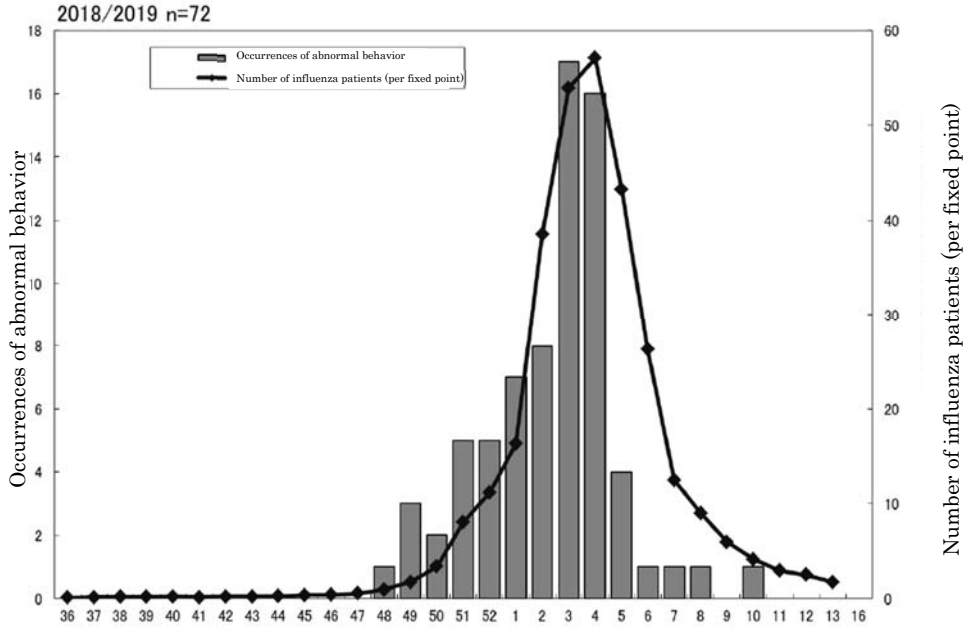

Figure 1-1: Investigation on the number and trend of occurrence of abnormal behavior (serious) (Figure 2-1 in the report)

	2018/2019
Day of onset	n (%)
Within 1 day Of fever onset	21 (30.00)
Day 2 of fever	42 (60.00)
Day 3	6 (8.57)
Day 4 -	1 (1.43)
	70 (100.00)

Unknown: 2

Figure 1-2: Number of days from fever onset to emergence of abnormal behavior
(Table 1-1 in the report)

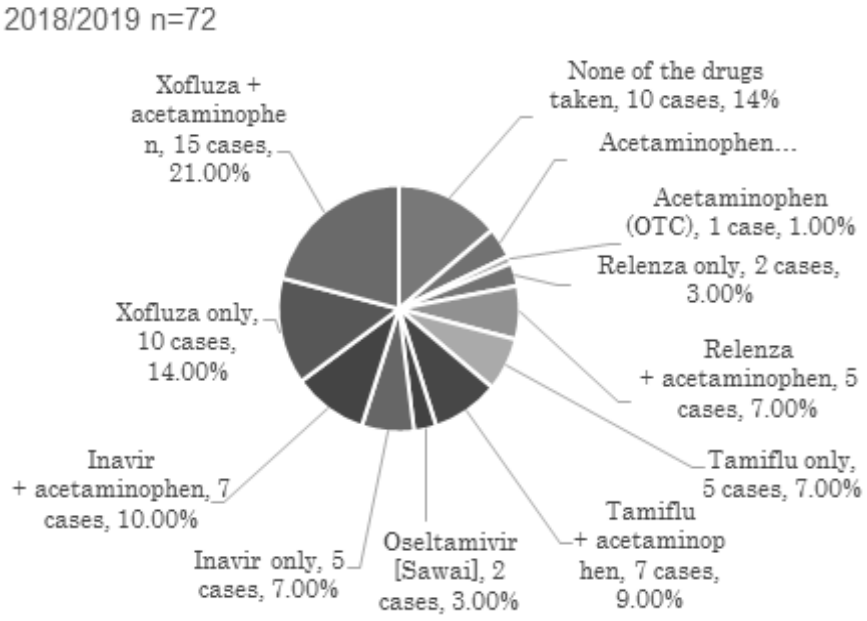

Figure 1-3: Combination of drugs taken (Figure 10-2 in the report)

(2) Cases of abnormal behavior and patient mortalities reported in association with influenza antiviral drugs

The number of abnormal behavior and patient mortalities associated with influenza antiviral drugs in the 2018/2019 season reported to PMDA from MAHs showed a trend almost comparable to the preceding seasons. A total of 55 patient mortalities were reported; however, causality with the suspected causative drugs could not be established or could not be assessed due to lack of sufficient information, etc. in all cases as a result of the assessment by experts.

3. Request for survey participation

The nationwide investigation of the state of instances of abnormal behavior in influenza-like-illness patients is continued this year. Given the importance of continued surveillance of instances of abnormal behavior when infected with influenza, two notifications entitled the Participation in Research for Nationwide Situation of Abnormal Behavior of Influenza-like-Illness Patients notification (request) (Joint HSIB No. 1127-1 and PSEHB/PSD Notification No. 1127-1 dated November 27, 2019, and Joint HSIB No. 1127-2 and PSEHB/PSD Notification No. 1127-2 dated the same) were issued to request participation of healthcare providers in the investigation, encouraging their understanding the objectives of this study and involvement in the accumulation of case data.

[References]

· Materials from the 9th Meeting of the Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council for FY 2019
https://www.mhlw.go.jp/stf/newpage_07535.html (only in Japanese)

· Comprehensive measures on influenza, Winter FY 2019:
https://www.mhlw.go.jp/bunya/kenkou/influenza/index.html (only in Japanese)

· Q & A on Influenza, FY 2019:
https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou01/qa.html
(only in Japanese)

2

Suspected Adverse Reactions to Influenza vaccines in the 2018 Season

1. Introduction

This section describes the status of instances of suspected adverse reactions to influenza vaccines reported from October 1, 2018 through April 30, 2019 (hereinafter referred to as the “2018 season”).

Medical institutions are required to report to MHLW when they encounter symptoms 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 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. Reports of Suspected Adverse Reactions to Influenza Vaccines (2018 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 amount of vaccines distributed to medical institutions.

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

	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 mortality reported	Number of reports (frequency)	Number of serious cases reported (frequency)	Number of patient mortality reported
52 511 510 (as of April 30, 2019)	53 (0.00010%)	0 (0%)	208 (0.00040%)	78 (0.00015%)	3 (0.0000057%)

* Reports by MAHs were of cases determined to be "serious" in accordance with Article 68-10 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 Preventative Vaccination Law (PV Law) or Article 68-10-2 of the PMD Act. (* and ** also apply to Tables 2 to 4.)

(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	26	92
Female	22	116
Unknown	5	0
Total	53	208

Table 3 Number of reports by age group

	Reports by MAHs		Reports by medical institutions		
Age group	Number of serious cases reported	Number of patient mortalities reported	Number of reports	Number of serious cases reported	Number of patient mortalities reported
0 - 9	16	0	61	24	1
10 - 19	2	0	16	8	0
20 - 29	5	0	11	3	0
30 - 39	6	0	27	6	0
40 - 49	3	0	16	5	0
50 - 59	5	0	16	6	0
60 - 69	2	0	15	7	0
70 - 79	4	0	32	11	1
80 or older	7	0	13	8	1
Unknown	3	0	1	0	0
Total	53	0	208	78	3

(3) Details of reported symptoms

Suspected adverse reactions to influenza vaccines reported during the 2018 season are outlined by System Organ Class (SOC) in the right columns of Table 4. There were no major changes compared with the 2017 season (October 1, 2017 to September 30, 2018).

A total of 3 cases of post-vaccination deaths were reported, of which causality with the suspected causative drugs was determined unclear for 2 cases citing worsening of underlying diseases or other factors as the possible causes and could not be assessed due to lack of sufficient information, etc. for 1 case as a result of the assessment by experts.

A total of 15 cases (Note 1) were reported as possible Guillain-Barre syndrome or acute disseminated encephalomyelitis (ADEM). Of these, 1 case, 2 cases, and 1 case respectively were determined to be of Guillain-Barre syndrome, of ADEM, and of Guillain-Barre syndrome and ADEM for which a causal relationship between the respective disease and the influenza vaccine could not be ruled out, according to expert opinions.

A total of 17 cases (Note 2) were reported as possible anaphylaxis. Of these, 9 cases were assessed as Level 3 or higher anaphylaxis using the Brighton Criteria (including 6 serious cases).

Regarding the number of reports from MAHs by manufacturing lot, there were no distinct concentration of reports of anaphylaxis found on specific lots.

At the Joint Meeting held in August 2019, it was concluded that there were no new concerns regarding safety of 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 terminology “Guillain-Barre syndrome” or “ADEM,” and those which are suspected to be Guillain-Barre syndrome or ADEM based on their clinical courses.

Note 2) Cases reported with the symptom name terminology “anaphylactic reaction,” “anaphylactic shock,” “anaphylactoid reaction,” or “anaphylactoid shock.”

Table 4 Comparison of the number of suspected adverse reaction reports between the 2017 and 2018 seasons (by SOC)

	2017 season †		2018 season ††	
	Tetravalent influenza vaccine (seasonal trivalent and H1N1)		Tetravalent influenza vaccine (seasonal trivalent and H1N1)	
SOC of symptom	Reports by MAHs	Reports by medical institutions (serious cases)	Reports by MAHs	Reports by medical institutions (serious cases)
Gastrointestinal disorders	7	11	3	7
General disorders and administration site conditions	34	39	20	31
Infections and infestations	12	17	8	8
Hepatobiliary disorders	9	5	3	3
Eye disorders	2	2	2	1
Musculoskeletal and connective tissue disorders	5	12	4	13
Blood and lymphatic system disorders	1	4	0	2
Vascular disorders	4	0	2	3
Respiratory, thoracic and mediastinal disorders	8	13	2	9
Ear and labyrinth disorders	0	1	0	0
Injury, poisoning and procedural complications	0	1	0	1
Cardiac disorders	1	6	1	3
Nervous system disorders	22	30	17	29
Renal and urinary disorders	7	6	2	3
Psychiatric disorders	0	0	1	0
Congenital, familial and genetic disorders	1	0	0	0
Metabolic and nutritional disorders	3	6	0	0
Pregnancy, puerperium and perinatal conditions	1	0	0	0
Skin and subcutaneous tissue disorders	16	11	10	18
Immune system disorders	5	11	4	7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1	0	0
Investigations	6	6	0	4
Total	144	182	79	142

† reported up to October 1, 2017 to September 30, 2018

†† reported up to October 1, 2018 to April 30, 2019

3. Future safety measures

As detailed in the Reporting Suspected Adverse Reactions for Routine Vaccination[2)] 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, based on the partial amendment of the enforcement rules of the PV Act dated September 27, 2019, acute generalised exanthematous pustulosis (AGEP) has been added to the adverse reaction reporting criteria for routine vaccination (see Reference: Suspected Adverse Reaction Reporting Criteria). Medical institutions are urged to continue to exercise caution in the 2019 season for the following issues concerning the onset of anaphylaxis:

(1) Vaccine recipients should be closely monitored for approximately 30 minutes after vaccination.
(2) If any symptoms suggestive of anaphylaxis are observed, appropriate measures should be taken.
(3) Vaccine recipients and their guardians should be advised to contact a physician immediately if any abnormalities are observed after vaccination.

MHLW/PMDA will continue their efforts to gather information concerning the safety of influenza vaccines including suspected adverse reaction reports 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: Distributed Material 8 for the Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council (the 42nd meeting) and the 2019 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (the 7th meeting) (Joint Meeting), Reports of Suspected Adverse Reactions to Influenza Vaccines
https://www.mhlw.go.jp/content/10906000/000541818.pdf (only in Japanese)

2) Reporting Suspected Adverse Reactions for Routine Vaccinations, etc.
Joint HSB Notification No. 0330-3 and No. 033-1, 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, dated March 30, 2013 (partially amended on July 16, 2014, September 26, 2014, November 25, 2014, and August 30, 2016, September 25, 2017, May 7, 2019, and September 27, 2019)
http://www.mhlw.go.jp/content/000552771.pdf (only in Japanese)

Report form
https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/hukuhannou_houkoku/dl/r01youshiki_02.pdf
(only in Japanese)
Entry instructions
https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/hukuhannou_houkoku/dl/r01youshiki_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>

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-Barre 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 strongly 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 Act 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)

3

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated December 3, 2019, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 Atezolizumab (genetical recombination)

Branded name (name of company)	a. Tecentriq for Intravenous Infusion 840 mg (Chugai Pharmaceutical Co., Ltd.) b. Tecentriq for Intravenous Infusion 1200 mg (Chugai Pharmaceutical Co., Ltd.)
Therapeutic category	Antineoplastics-miscellaneous
Indications	a. PD-L1-positive, hormone receptor-negative and HER2-negative inoperable or metastatic breast cancer b. Unresectable, advanced or recurrent non-small cell lung cancer, extensive-stage small cell lung cancer

PRECAUTIONS (revised language is underlined)

[Under old instructions]	
ADVERSE REACTIONS (Clinically Significant Adverse Reactions) (newly added)	**Haemophagocytic syndrome:** Haemophagocytic syndrome 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]	
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions) (newly added)	Haemophagocytic syndrome
Reference information	Number of cases (for which a causal relationship between the drug and event could not be ruled out) reported during the previous approximately 18-month period (April 2018 to September 2019) Cases involving haemophagocytic syndrome: 6 (1 instance of patient mortality) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 4 000 Japanese market launch: April 2018

Case summary 1

No.	Patient		Daily dose and administration duration	Adverse reaction
	Sex/ age	Indication for use (Complication)		Clinical course and treatment provided
1	Female 70s	Large cell lung cancer (varicose veins of lower extremities, hepatic steatosis, emphysema, oesophageal hiatal hernia)	1200 mg/dose every 3 weeks 1 day	**Haemophagocytic syndrome** Stage IV Metastasis sites: Brain (left upper frontal lobe, right cerebellar hemisphere, upper vermis, left temporal lobe) lymph node (left axillary mass lymph node) Prior treatment: chemotherapy was performed as the first line treatment History of radiotherapy: radiation site; brain, total radiation dose; 30 Gy Medical history: left subclavian artery stenosis, gastric cancer, cerebellar infarction Miscellaneous: No familial history of haemophagocytic syndrome Day 1 of administration (Day of termination): Administration of atezolizumab was initiated as the second line treatment (no more administration thereafter) (PD-L1: >1%) 7 days after termination: Drug eruption (Grade 2) appeared. The eruption was resolving with corticosteroid and antihistamine. 13 days after termination: Drug eruption appeared. The patient recovered from the eruption with corticosteroid 17 days after the termination of atezolizumab. 21 days after termination: The patient developed fever close to 39°C. Pyometra was suspected and ceftriaxone sodium hydrate was administered. Obstetrician and gynecologist was consulted and agreed that there was no pus. Hydrometra (Grade 1 at the worst) Treatment: intravenous ceftriaxone sodium hydrate 1 g×2/day, intravenous tazobactam/piperacillin 4.5 g×3/day 24 days after termination: 2 types of blood cells (White blood cells and platelets) decreased. Disseminated intravascular coagulation syndrome (Grade 2 at the worst) was suspected and thrombomodulin alfa (genetical recombination) (IV) was administered. Thrombocytopenia observed (Grade 3). 10 units platelets were infused. 26 days after termination: The patient was switched from ceftriaxone sodium hydrate to meropenem hydrate and the patient received the latter. 27 days after termination: Ferritin increased to 17 800 ng/mL. Hematology department was consulted. Possibility of bone marrow infiltration was indicated. 28 days after termination: Haemophagocytic syndrome was also suspected and dexamethasone sodium phosphate was administered, 6.6 mg×3 vials (20 mg/day for 4 days, followed by 10 mg/day for 4 days, then by 5 mg/day for 4 days, and by 4 mg/day thereafter.) 29 days after termination: Bone marrow biopsy was performed. Pathology department denied bone marrow infiltration. Haemophagocytic syndrome was improved with corticosteroid administration. 31 days after termination: LDH was 1 800 IU/L. 33 days after termination: Haemophagocytic syndrome was diagnosed (Grade 2 at the worst). 40 days after termination: The patient recovered from haemophagocytic syndrome and

				46 days after termination 59 days after termination	disseminated intravascular coagulation syndrome. Hydrometra was resolved Betamethasone 4 mg was prescribed as tapering of corticosteroid and the patient was transferred to another hospital. [Cross reference with the diagnostic criteria* of hemophagocytic lymphohistiocytosis (HLH)] HLH is diagnosed if 1 or 2, and 3 are met.

1. Molecular pathological diagnosis	Not performed
2. Or 3/4 or more of the following are met.	
Pyrexia	Yes
Splenomegaly	No
Reduction in 2 or more types of blood cell counts	Yes
Hepatitis-like findings	Yes
3. In addition to the above, 1/4 or more of the following are met.	
Haemophagocytosis image	Yes
Elevated levels of ferritin	Yes
Elevated levels of soluble IL-2 receptor	Yes
Decrease or loss of NK cell activity	Yes
4. Others supporting diagnosis	
Hypertriglyceridaemia	Yes
Hypofibrinogenaemia	No
Hyponatraemia	Yes

Yes, deviation from relevant criteria; No, Null/negative test results

*Alexandra H. Filipovich. Hemophagocytic lymphohistiocytosis (HLH) and related disorders.Hematology.2009:127-131

Clinical diagnosis: Haemophagocytic syndrome

Histopathology report: Bone marrow, clot and biopsy

Hypocellular marrow

Bone marrow clot and biopsied tissue: Marrow hypoplasia with approximately 10-20% cell density and M/E ratio approximately 1-2:1. All 3 types of haematopoietic cells maintained maturing tendency. Immunostaining revealed no findings suggestive of cancer infiltration. With macrophage pronounced, the results do not contradict a diagnosis of haemophagocytic syndrome.

Laboratory test values

	143 days before administration	7 days after termination	24 days after termination	25 days after termination	27 days after termination	28 days after termination	33 days after termination	42 days after termination
Plt ($\times 10^4$/μL)	33.3	26.4	3	2.5	9.3	7.4	3.4	12
WBC ($\times 10^3$/μL)	7.67	6.74	3.16	3.6	3.34	2.49	3.14	6.64
Hb (g/dL)	11.9	11	12.4	12.1	11.7	10.8	10.2	11
RBC ($\times 10^4$/μL)	402	354	413	399	387	359	347	362
MCV (fL)	89.3	93.8	89.8	89	88.6	88.9	89.3	92
MCH (pg)	29.6	31.1	30	30.3	30.2	30.1	29.4	30.4
MCHC (%)	33.1	33.1	33.4	34.1	34.1	33.9	32.9	33
AST (IU/L)	17	17	366	290	307	297	118	41
ALT (IU/L)	10	16	66	59	70	66	62	62
γ-GTP (IU/L)	11	—	—	—	—	—	—	—
TG (mg/dL)	96	—	—	—	—	238	—	—
Serum FER (ng/mL)	—	—	—	—	17 800	—	—	—
Soluble IL-2 receptor (U/mL)	—	—	—	—	—	1 280	—	—
FDP (μg/mL)	2.8	—	866.2	—	272.5	—	—	—
Fbg (mg/dL)	337.9	—	161.9	—	224.5	—	—	—
PT Ratio	1.02	—	1.04	—	—	—	—	—
NK cell activity (%)	—	—	—	—	—	24	—	—
EBV antibody test	—	—	—	—	—	geniQ EBV <2 $\times 10^2$ copies/mL	—	—
Anti-nuclear antibody	—	—	—	—	—	—	—	—

Concomitant drugs: None

Case summary 2

No.	Patient		Daily dose and administration duration	Adverse reaction	
	Sex/ age	Indication for use (Complication)		Clinical course and treatment provided	
2	Male 50s	Lung adenocarcinoma (pleural effusion, increased carcinoembryonic antigen, hepatic steatosis)	1200 mg/dose every 3 weeks 1 day	**Haemophagocytic syndrome** Metastasis sites: bone, lymphatic node, lung Prior treatment: cisplatin + pemetrexed sodium hydrate as adjuvant chemotherapy for first episode Carboplatin + pemetrexed sodium hydrate +bevacizumab (genetical recombination) for recurrence Smoking history: 20/day from 20s to 40s	
				Day 1 of administration (Day of termination)	Administration of atezolizumab was initiated (no more administration thereafter) Chest X ray revealed no pneumonitis findings. The patient had temporal pyrexia but went home with no episodes.
				1 day after termination	The patient had a slight fever; 37°C. Vital signs were normal and the patient wend home.
				7 days after termination	Fever started in the evening.
				8 days after termination	Pyrexia (38.3°C) developed at dawn. The patient visited the respiratory department outpatient in the morning and was prescribed acetaminophen for the condition. No abnormalities were noted in the chest X ray. CRP was 0.4 mg/dL, Plt was 13.8×10^4/μL Pyrexia (40.0°C) developed at home at night and the patient visited the emergency outpatient unit. Pyrexia and decreased Plts were confirmed in the visit. The conditions were determined to be adverse events and the patients was sent home to be monitored for his clinical course.
				9 days after termination	The patient visited the respiratory department due to 38°C pyrexia. The chest X ray and CT scan were normal (no findings suggestive of interstitial pneumonia) CRP was 2.90 mg/dL, Plt was 10.2×10^4/μL. Celecoxib was prescribed. The patient was sent home to be monitored for his clinical course.
				10 days after termination	Right neck pain, hepatic impairment developed.
				11 days after termination	Left neck pain also developed in addition to the right neck pain._ Marked decreases in Plt and high CRP values were observed. Pyrexia at 37.8°C developed. The patient visited the emergency outpatients department at around 16:00. Cervical adenitis and general malaise were confirmed. Plt was 3×10^4/μL.
				12 days after termination	Plt was 1.8×10^4/μL. Disseminated intravascular coagulation syndrome was suspected and nafamostat

					mesilate was administered.
				13 days after termination	Loss of consciousness occurred in the morning. CRP was 18 mg/dL, Plt was 1.7 $\times 10^4$/μL, AST was 309 IU/L. Depressed level of consciousness and splenomegaly were observed and steroid-pulse therapy was performed. Non-cardiogenic pulmonary oedema onset in the evening. Generalized rigid convulsion occurred and resolved with an anticonvulsant. Disturbed consciousness was not improved. Disturbed consciousness, pyrexia, left neck pain suggested encephalitis but cerebrospinal fluid tests could not be performed due to the complicating convulsion. Echocardiogram: EF32%. No left or right-sided expansion was identified. IVC 9/5 mm of breathing variation was observed. [Antibody test results] IgG, 1045; IgA, 218; IgM, 71; C3, 80; C4, 44; antinucleat antibody, <40
				14 days after termination	AST was 613 IU/L. Oliguria occurred and the patient had 40 < fever. Steroid pulse therapy was performed. The patient respond to steroid pulse therapy only for a few hours and very prone to pyrexia. A chest CT scan identified opacities. Serious acute respiratory distress syndrome, decerebrate rigidity (irreversible brain stem invasion) led to multi-organ failure (Grade 4). Echocardiogram: IVC 10 mm, congestive liver (-), left ventricular compression findings in the visible scope (-) Prerenal disorder was unlikely. Without hydronephrosis, postrenal disorder was also unlikely. Midazolam and diazepam were administered as palliative treatment.
				15 days after termination	Multi-organ failure has progressed. Steroid pulse therapy was performed twice. Cerebrospinal fluid tests were performed. [Test results] Xanthochromia, +; opacification, -; Bloodiness, -; sedimentation, - Smear test, WBC small; Indian ink staining, -; Gram staining, no bacteria were found. Culture and identification, bacteria, -; fungi, -; anaerobe, - Susceptibility: Bacteria, -; fungi, -; anaerobe, - [findings suggestive of haemophagocytic syndrome] ・central nervous system symptoms

				・cerebrospinal fluid: cell count or protein increased.
			16 days after termination	The patient was confirmed dead. [Autopsy findings] ・Haemophagocytic image was identified in the neck-posterior mediastinal node, spleen, bone marrow, and hepatic sinus_ No organs across the body presented lymphocytic infiltration suggestive of autoimmune diseases. No significant pathogens were detected by comprehensive pathogen search. ・No microclots were observed. There were no findings of disseminated intravascular coagulation syndrome either. Diagnosis by the pathologist haemophagocytic syndrome

Laboratory test values

B.A: Before administration A.T.: After termination	7 days B.A.	8 days A.T.	9 days A.T	11 days A.T.	12 days A.T.	13 days A.T.	14 days A.T.	15 days A.T.
Plt (×10^4/μL)	18.1	13.8	10.2	3	1.8	1.7	1.1	2.9
WBC (×10^3/μL)	5.17	5.28	3.75	2.96	2.86	2.70	7.44	11.34
Hb (g/dL)	14.8	15.5	15.8	16.0	15.9	16.0	15.9	16.2
RBC (×10^4/EDF)	420	441	451	461	460	464	464	467
MCV (fL)	102.1	102.5	100.9	100.9	100.9	99.4	94.4	99.4
MCH (pg)	35.2	35.1	35	34.7	34.6	34.5	34.3	34.7
MCHC (%)	34.5	34.3	34.7	34.4	34.3	34.7	36.3	34.9
AST (IU/L)	56	33	33	95	205	309	613	598
ALT (IU/L)	103	48	45	88	167	218	391	349
γ-GTP (IU/L)	403	312	312	664	779	772	977	1 004
TG (mg/dL)	—	—	—	—	—	—	217	—
Serum FER (ng/mL)	—	—	—	—	—	—	30 804	—
Soluble IL-2 receptor (U/mL)	—	—	—	—	—	—	11 900	—
FDP (μg/mL)	—	—	—	—	90.5	—	—	—
Fbg (mg/dL)	—	—	—	—	314	—	278	—
PT Ratio	—	—	—	—	1.14	1.14	1.02	—
NK cell activity	—	—	—	—	—	—	—	—
EBV antibody test	—	—	—	—	—	—	EBV-VCA-IgG was 5.2 (+) EBV-VCA-IgM 0.1 (-) EBV-EBNA 0.3 (-) (EBV DNA 2.1×10^2 copies/106cells)	—
Anti-nuclear antibody	—	—	—	—	—	<40	—	—
CRP (mg/dL)	0.18	0.4	2.9	—	15.15	18.11	18.66	8.13

Concomitant drugs: Retinol/calciferol combination drug, precipitated calcium carbonate/cholecalciferol/magnesium, esomeprazole magnesium hydrate, magnesium hydroxide, brotizolam

2 Osimertinib mesilate

Branded name (name of company)	Tagrisso Tablets 40 mg, 80 mg (AstraZeneca K.K.)
Therapeutic category	Antineoplastics-miscellaneous
Indications	EGFR gene mutation-positive inoperable or recurrent non-small cell lung cancer

PRECAUTIONS (revised language is underlined)

[Under new instructions]

11. ADVERSE REACTIONS

11.1 Clinically Significant Adverse Reactions) (newly added)

Congestive cardiac failure and decreased left ventricular ejection fraction

Reference information

Number of cases (for which a causal relationship between the drug and event could not be ruled out) reported during the previous approximately 41-month period (May 2016 to September 2019)
Cases involving cardiac failure: 5 (No patient mortalities)
Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 15 000
Japanese market launch: May 2016

Case summary

No.	Patient		Daily dose Treatment duration	Adverse reactions	
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female 70s	Non-small cell lung cancer (none)	80 mg for 206 days	**Congestive cardiac failure, decreased left ventricular ejection fraction** Allergy history, adverse drug reaction history, family history, non-drug concomitant, exposure to radiation, drugs administered prior to the diagnosis with heart disorder, past adverse reaction history, smoking history, drinking history: none	
				20 months before administration	Dyspnoea and pleural effusion were noted. Echocardiography: no abnormality was revealed, EF:59% Non-small cell lung cancer was diagnosed.
				604 days before administration	BNP: 25.5 pg/mL
				558 days before administration	BNP:10.0 pg/mL
				551 days before administration	The patient visited the hospital for the first time, referred from other hospital for a detailed examination of right pleural effusion. The patient was diagnosed with primary lung adenocarcinoma stage IV, cT1cN0M1a based on the pleural fluid analysis and the biopsy for tumor of pleura. Tumor sites: lung (right lower lobe), Pleural effusion.
				537 days before administration	EGFR gene mutation (Exon 19 deletion) results were positive. Gefitinib 250 mg was initiated.

				2 weeks before administration	Increases in pleural effusion were observed. The tumor was judged to be PD (progressive disease). Thoracentesis was difficult and plasma test was performed instead. The patients tested T790M positive.
				1 day before administration	Gefitinib was discontinued. ECG (arrhythmia, ischaemia etc.): no abnormality
				Day 1 of administration	Osimertinib mesilate 80 mg/day was initiated as the 2nd line.
				Date unknown	After that, the patient's clinical course went uneventful with no particular adverse events, remained on PR (partial response).
				Day 190 of administration	Chest X-ray: no abnormalities, SpO2: 96% (room air)
				Month 7 of administration	Exertional dyspnea developed.
				Day 204 of administration	The patient visited the hospital due to the worsening of symptoms and was admitted for detailed exam. X-ray and CT scan showed a retention of right pleural effusion, cardiomegaly, congestive cardiac failure, and decreased left ventricular ejection fraction. Symptoms: Shortness of breath, dyspnea, orthopnoea/dyspnoea paroxysmal nocturnal, Increases in pleural effusion Physical findings: cold extremities Severity classification of cardiac failure: Ⅱ(Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain) Signs of cancer progression: none
				Day 206 of administration	The patient re-visited the hospital. BNP: 763.6 pg/mL, SpO2: 92% (room air） Echocardiography showed left ventricular enlargement, circumferential decrease in systolic function, EF:19%, ECG (arrhythmia, ischaemia etc.) no abnormalities. The patient was admitted to the hospital for cardiology. Enzyme was administered on the same day. Intravenous diuretics (furosemide 20 mg once daily) was started. EF was unknown with no measurements prior to admission.) CPK-MB: 6 U/L, troponin I: 20 pg/mL, Sugar blood level: 120 mg/dL
				Day 207 of administration (Day of discontinuation)	Oral administration of osimertinib mesilate was discontinued.
				1 day after discontinuation	Oral co-administration of β-Blocker (Carvedilol tablets 1.25 mg) was started.
				9 days after discontinuation	EF was 19%
				10 days after discontinuation	Furosemide 20 mg once daily was switched to torasemide OD tab. 4 mg.
				13 days after discontinuation	Symptom improvement was observed. Pleural fluid was withdrawn. There was

				14 days after discontinuation 27 days after discontinuation 46 days after discontinuation 69 days after discontinuation 90 days after discontinuation 111 days after discontinuation 139 days after discontinuation 150 days after discontinuation	no problem in the cardiac catheter test. The patient was discharged (EF: 19%). EF was 25%, BNP 252.2 pg/mL. BNP was 227.1pg/mL. Congestive cardiac failure was recovering. Decreased Left ventricular ejection fraction was resolving. EF was 21%, BNP 91.3 pg/mL. BNP was 48.3 pg/mL. EF was 33%. BNP was 70.8 pg/mL. EF was 32%.
	Suspected concomitant drugs: none Concomitant drugs: retinol/calciferol combination drug, nipradilol, fluorometholone				

Laboratory test values

Test items (unit)	604 days before administration	558 days before administration	1 day before administration	Day 204 of administration	Day 206 of administration	27 days after discontinuation	69 days after discontinuation
Highest body temperature (Cel)	—	36.2	36.2	—	36.6	36.3	36.2
Pulse (times/min)	—	70	80	—	66	60	66
B Systolic blood pressure (mmHg)	—	120	110	—	98	102	112
BDiastolic blood pressure (mmHg)	—	60	60	—	60	60	80
WBC (/mm^3)	—	6 300	6 400	6 700	5 600	4 500	4 300
RBC (10*4/mm^3)	—	494	435	368	383	368	382
Hb (g/dL)	—	14.5	12.9	11.0	11.5	11.0	11.3
Haematocrit (%)	—	44.4	38.9	33.9	35.3	32.8	35.0
Plt (10*4/mm^3)	—	28.5	27.4	16.7	17.3	16.1	18.8
CEA (ng/mL)	—	—	—	1.7	—	—	—
KL－6 (U/mL)	—	—	—	301	—	—	—
Total protein (g/dL)	—	7.1	7.3	6.3	6.5	6.5	6.6
Albumin (g/dL)	—	3.8	4.2	3.6	3.7	3.7	3.8
Total bilirubin (mg/dL)	—	0.6	0.6	0.6	0.6	0.5	0.6
Direct bilirubin (mg/dL)	—	0.1	—	—	—	—	—
Na (meq/L)	—	—	139	140	140	140	138
K (meq/L)	—	—	4.4	3.7	4.0	4.0	4.7
Cl (meq/L)	—	—	108	108	107	105	106
BUN (mg/dL)	—	12	13	10	8	9	14
Serum creatinine (mg/dL)	—	0.53	0.60	0.69	0.60	0.60	0.75
Ca (mg/dL)	—	—	9.5	8.9	8.8	—	—
eGFR (mL/min/1.73m^2)	—	—	73.2	62.8	73.2	—	—
AST (U/L)	—	68	24	24	25	17	25
ALT (U/L)	—	69	14	14	14	7	14
LDH (U/L)	—	294	275	228	229	195	191
ALP (U/L)	—	504	329	196	219	191	236
γ－GTP (U/L)	—	121	29	—	30	—	—
CPK (U/L)	—	—	—	126	121	72	58
CPK－MB (U/L)	—	—	—	—	6	—	—

Amylase (U/L)	—	—	—	81	83	—	—
CRP (mg/dL)	—	0.34	0.10	0.04	0.19	0.02	0.05
SP－D (ng/mL)	—	—	—	21.7	—	—	—
SLX (U/mL)	—	—	—	34	34	34	36
Blood sugar (mg/dL)	—	108	112	—	120	—	—
Erythroblasts (/100WBC)	0.0	—	—	—	—	—	—
HbA1c (%)	5.6	—	—	—	—	—	—
TSH (μiU/L)	4.18	—	—	—	3.430	—	—
FT3 (pg/mL)	2.75	—	—	—	1.80	—	—
Free T4/FT4 (ng/dL)	1.22	—	—	—	1.40	—	—

Other Laboratory Test Results

<Date unknown>
Weight: 43.7 kg, BMI: 18.5-24.9
<597 days before administration >
Echocardiography
【Left ventricular】LVDd: 44 mm, LVDs: 30 mm, IVST: 9 mm, LVPWT: 9 mm, EF (simpson' s): 59%, FS: 32%
【Left atrial】LAD: 25 mm
【Left ventricular inflow blood waveform】E wave: 57 cm/sec, A wave: 98 cm/sec, E/A: 0.58, DCT: 169 msec
【Aorta】LVOT (annulus dimension): 20 mm, valsalva sinus diameter: 33 mm, diameter of ST-junction: 26 mm, diameter of ascending Ao: 31 mm
【Aortic valve】AR: slight, LV-Ao max PG: 7 mmHg, LV-Ao mean PG: 3 mmHg
【Mitral valve】MR (-) : slight
【Tricuspid valve】TR: slight, presumed systolic RV pressure: 25 mmHg, presumed RA pressure: 5 mmHg
【IVC】IVC diameter: 6 mm, respiratory variation: ±
【P-Valve】PR: slight
【Pericardial effusion】+
【Pleural effusion】right: +++, left: -
【Findings】
LV wall motion, posterior septal root, middle wall infarction, apical part showed hypokinesis. EF: lower limits of normal – around 59%, cavity size：W.N.L
AV: valve cusp calcification (+), Expansion limit (-), AR：slight, from middle junction MR: slight TR：slight, presumed systolic RV pressure: 20+ (RA：5) = 25 mmHg PR：slight, presumed PA end-diastolic pressure: 6+(RA：5)= 11 mmHg IVC= 6 mm respiratory variation (±)
Pericardial effusion: RA side 9 mm collapse (-) Pleural effusion: Rt (+++), Lt (-), echo free space in the spleen (+)
<9 days after discontinuation>
Echocardiography
Disease name: Congestive cardiac failure
【Findings】
EF: 19%, E/A: 1.0, Dct: 171 msec
Left atrial: enlargement (-), 36.0 mm 39.4×56.0 mm (4CV) MR: mild
Left atrial: enlargement (+), 59.2 mm AR：mild
Right atrial: enlargement (-), 32.0×44.0 mm (4CV) TR：mild
Right ventricular: enlargement (-), PR: mild
IVC: no expansion, respiratory variation, 12.1 mm (expiration), RVSP: 18.5 mmHg
Mitral valve: hypertrophy in both valve cusps (+), LV inflow: 0.8 m/s
Aortic valve: hypertrophy in annular part and tricuspid (+), Ao Vmax: 1.1m/s, Ao max PG: 4.8 mmHg, Ao mean PG: 3.0 mmHg, AVA (Doppler): 1.75 cm^2, 1.30 cm^2/m^2
LVH: no left ventricular hypertrophy, LVOT Vmax: 0.7 m/s, max PG: 1.8 mmHg
LV Wall motion: diffuse severe hypokinesis
Pericardial effusion: none, Pleural effusion: none, Thrombus: none, Wart: none, Shunt: none
【Comment】Electrocardiogram: N.S.R
【Diagnostic ultrasound】DCM-like features were observed. LV systolic function decreased significantly. LV expansion was observed. Overload findings related to the right ventricular were not observed.
【Mmode/2D Method】M MODE LAD: 39.2 mm, AOD: 31.9 mm, LVIDd: 63.5 mm, LVIDs: 57.8 mm, IVST: 7.3 mm PWT: 7.3 mm, EDV：205 ml, ESV: 165 ml, SV: 39 ml, EF: 19%, FS: 9% IVC (expiration): 12.1 mm
【Biplane Simpson Method】LV EDV: 155 ml, LV ESV: 130 ml, SV: 25 ml, EF: 16%
【LV inflow】E wave: 77 cm/s, A wave: 78 cm/s, E/A: 1.0, Dct: 171 msec
【TDI】e'(late): 6.0 cm/s, E/e': 12.8
【LV outflow】Vmax: 0.7 m/s, max PG: 1.8 mmHg, mean PG: 0.9 mmHg, VTI: 11.9 cm, Dimension: 1.9 cm
【Aortic Valve】Vmax: 1.1m/s, max PG: 4.8 mmHg, mean PG: 3.0 mmHg, VTI: 20.0 cm, AVA (Doppler) (3-5): 1.75 cm^2, AVA Index (Doppler): 1.30 cm^2/m^2
【Tricuspid Valve】TRPG: 18.5 mmHg
【Pulmonary Valve】Vmax: 0.5 m/s

3 Bilastine

Branded name (name of company)	Bilanoa Tablet 20 mg (Taiho Pharmaceutical Co., Ltd.)
Therapeutic category	Allergic agents-miscellaneous
Indications	Allergic rhinitis, urticaria, itching accompanying cutaneous disease (eczema and dermatitis, cutaneous pruritus)

PRECAUTIONS (revised language is underlined)

[Under old instructions]

ADVERSE REACTIONS (Clinically Significant Adverse Reactions) (newly added)	Shock, anaphylaxis: Shock or anaphylaxis 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.
Reference information	Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported in approximately the previous 34-month period (November 2016 to August 2019). Cases involving shock, anaphylaxis: 3 (no patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 2 600 000 Launched in Japan: November 2016

Case summary

No.	Patent		Daily dose and administration duration	Adverse reaction
	Sex/age	Indication for use (complications)		Clinical course and treatment provided
1	Female, 50s	Atopic dermatitis (none)	20 mg for 1 day ↓ Discontinued	**Anaphylaxis** History: face oedema associated with loxoprofen sodium hydrate Day 1 of administration (Day of discontinuation): Bilastine 20 mg was administered for atopic dermatitis before bed. Palmar diffuse erythema was found bilaterally 15 to 20 minutes later. Erythema then expanded over the whole body. Symptoms such as oedema, tremor, dyspnoea appeared. The patient was transported by ambulance. Symptoms were improved by emergency treatment (details unknown). The patient was admitted to the hospital for close monitoring. Concomitant drugs were all discontinued. 2 days after discontinuation: The patient was discharged from the hospital. Bilastine has not been resumed since.
	Suspect concomitant drugs: None Concomitant drugs: Heparin-like substances, white petrolatum, tacrolimus hydrate, dexamethasone, betamethasone valerate/ gentamicin sulfate, zinc oxide			

4

Revision of Precautions (No.309)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated December 3, 2019.

1 Hormones-miscellaneous

Mecasermin (genetical recombination)

Branded name	Somazon 10 mg for Injection (OrphanPacific, Inc.)
[Under Old instructions]	
Precautions concerning Indications (newly added)	This drug should be administered only if the therapeutic benefits to patients are considered to outweigh the associated risks taking account the following: •Although causality is unclear, benign and malignant tumors have been reported to occur in patients during or after the completion of treatment with mecasermin in Japan and overseas. ·Mammary gland tumour including adenocarcinoma has been reported to occur as observed in an animal study that administered this drug to SD rats for 53 weeks.
Important Precautions	(deleted) note 1 Note 1: The current language ”This drug should be administered only if the therapeutic benefits to patients are considered to outweigh the associated risk because mammary gland tumour including adenocarcinoma has been reported to occur as observed in an animal study that administered this drug to SD rats for 53 weeks.” should be deleted.

2 Antineoplastics-miscellaneous

Atezolizumab (genetical recombination)

Branded name	Tecentriq for Intravenous Infusion 840 mg, 1200 mg (Chugai Pharmaceutical Co., Ltd.)
[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)	**Haemophagocytic syndrome**: Haemophagocytic syndrome 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]	
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions (newly added)	Haemophagocytic syndrome

3 Antineoplastics-miscellaneous

Osimertinib mesilate

Branded name	Tagrisso Tablets 40 mg, 80 mg (AstraZeneca K.K.)
[Under New instructions]	
11. ADVERSE REACTIONS	
11.1 Clinically Significant Adverse Reactions (newly added)	Congestive cardiac failure and decreased left ventricular ejection fraction

4 Allergic agents-miscellaneous

Bilastine

Branded name	Bilanoa Tablet 20 mg (Taiho Pharmaceutical Co., Ltd.)
[Under Old instructions]	
Adverse Reactions (Clinically Significant Adverse Reactions) (newly added)	**Shock, anaphylaxis**: Shock or anaphylaxis 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.

5

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for newly-approved drug products refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. The MAH responsible for a new drug in the EPPV period is required to collect adverse drug reactions (ADRs) data from all medical institutions where the drug is used and to take safety measures as appropriate. The aim of EPPV is to promote the rational and appropriate use of drugs in medical treatments and to facilitate prompt action for the prevention of serious ADRs. EPPV is specified as a condition of product approval.

(As of 30 November, 2019)

◎: Products for which EPPV was initiated after November 1, 2019

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Vortioxetine hydrobromide Trintellix Tablets 10 mg, 20 mg	Takeda Pharmaceutical Company Limited.	November 27, 2019
◎	Necitumumab (genetical recombination) Portrazza Injection 800 mg	Nippon Kayaku Co., Ltd.	November 22, 2019
◎	Ranibizumab (genetical recombination) *1 Lucentis solution for intravitreal injection 10mg/mL	Novartis Pharma K.K.	November 22, 2019
◎	Ixekizumab (genetical recombination) *2 Taltz Subcutaneous Injection Syringes 80 mg, Taltz Subcutaneous Injection Autoinjectors 80 mg	Eli Lilly Japan K.K.	November 22, 2019
◎	Venetoclax Venclexta Tablets 10 mg, 50 mg, 100 mg	AbbVie GK	November 22, 2019
◎	Safinamide mesilate Equfina Tablets 50 mg	Meiji Seika Pharma Co., Ltd.	November 20, 2019
◎	Roxadustat Evrenzo tablets 20 mg, 50 mg, 100 mg	Astellas Pharma Inc.	November 20, 2019
◎	Ivabradine hydrochloride Coralan Tablets 2.5 mg, 5 mg, 7.5 mg	Ono Pharmaceutical Co., Ltd.	November 19, 2019
	Quizartinib hydrochloride Vanflyta Tablets 17.7 mg, 26.5 mg	Daiichi Sankyo Co., Ltd.	October 10, 2019
	Insulin degludec (genetical recombination)/liraglutide (genetical recombination) Xultophy combination Injection FlexTouch	Novo Nordisk Pharma Ltd.	September 26, 2019
	Belimumab (genetical recombination) Benlysta for I.V. infusion 120 mg, 400 mg	Glaxo Smith Kline K.K.	September 20, 2019
	Apremilast*3 Otezla Tablets 10 mg, 20 mg, 30 mg	Celgene K.K.	September 20, 2019
	Desmopressin acetate hydrate*4	Ferring Pharmaceuticals	September 20,

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Minirinmelt OD Tablets 25 μg, 50 μg	Co., Ltd.	2019
Azithromycin hydrate Azimycin Ophthalmic Solution 1%	Senju Pharmaceutical Co., Ltd.	September 11, 2019
Blonanserin Lonasen Tape 20 mg, 30 mg, 40 mg	Sumitomo Dainippon Pharma Co., Ltd.	September 10, 2019
Patisiran sodium Onpattro infusion 2 mg/mL	Alnylam Pharmaceuticals, Inc.	September 9, 2019
Glycopyrronium bromide/formoterol fumarate hydrate Bevespi Aerosphere 28 inhalations	AstraZeneca K.K.	September 4, 2019
Budesonide/glycopyrronium bromide/formoterol fumarate hydrate Breztri Aerosphere 56 inhalations	AstraZeneca K.K.	September 4, 2019
Entrectinib Rozlytrek Capsules 100 mg, 200 mg	Chugai Pharmaceutical Co., Ltd.	September 4, 2019
Defibrotide sodium Defitelio Injection 200 mg	Nippon Shinyaku Co., Ltd.	September 4, 2019
Ravulizumab (genetical recombination) Ultomiris Intravenous Infusion 300 mg	Alexion Pharmaceuticals, Inc.	September 4, 2019
pH4-treated normal human immunoglobulin Privigen 10% I.V. Drip Infusion 5 g/50 mL, 10 g/100 mL, 20 g/200 mL	CSL Behring K.K.	August 19, 2019
Freeze-dried inactivated tissue culture rabies vaccine Rabipur for intramuscular injection	Glaxo Smith Kline K.K.	July 26, 2019
Darunavir ethanolate/cobicistat/emtricitabine/tenofovir alafenamide fumarate Symtuza Combination Tablets	Janssen Pharmaceutical K.K.	July 26, 2019
Peficitinib hydrobromide Smyraf Tablets 50 mg, 100 mg	Astellas Pharma Inc.	July 10, 2019
Ceftolozane sulfate/tazobactam sodium Zerbaxa Combination for Intravenous Drip Infusion	MSD K.K.	June 25, 2019
Guanfacine hydrochloride*5 Intuitive Tablets 1 mg, 3 mg	Shionogi & Co., Ltd.	June 18, 2019
Romiplostim (genetical recombination)*6 Romiplate for s.c. injection 250 μg	Kyowa Hakko Kirin Co., Inc	June 18, 2019
Tocilizumab (genetical recombination)*7 Actemra Intravenous Infusion 80 mg, 200 mg, 400 mg	Chugai Pharmaceutical Co., Ltd.	June 12, 2019
Sodium selenite Aselend Injection 100 μg	Fujimoto Pharmaceutical Corporation	June 6, 2019

*1 Retinopathy of prematurity

*2 Ankylosing spondylitis with inadequate response to existing therapies

*3 Oral ulcers associated with Behçet's disease with inadequate response to local therapies

*4 Nocturia due to nocturnal polyuria in males

*5 Attention deficit/hyperactivity disorder (AD/HD) in adult patients
*6 Aplastic anemia inadequately controlled with existing therapies
*7 Cytokine release syndrome induced by tumor-specific T cell infusion treatment