Pharmaceuticals and Medical Devices Safety Information

No. 388 December 2021

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* publication is issued reflective of safety information collected by the Ministry of Health, Labour and Welfare (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) Medical Product Information web page (http://www.pmda.go.jp/english/index.html) and on the MHLW website (http://www.mhlw.go.jp/, only available in Japanese language).

Available information is listed here

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

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

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No. 388 December 2021

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, 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 medical and pharmaceutical providers, 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
EPPV	Early Post-marketing Phase Vigilance
HSB	Health Service Bureau
irAE	immune related adverse event
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
MRCP	Magnetic resonance cholangiopancreatography
PMDA	Pharmaceuticals and Medical Devices Agency
PMD Act	Act on Securing Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices
PS	Performance Status
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
PV Law	Preventative Vaccination Law
SOC	System Organ Class

1
Suspected Adverse Reactions to Influenza Vaccines in the 2020 Season

1. Introduction

This section describes the status of instances of suspected adverse reactions to influenza vaccines reported from October 1, 2020 through March 31, 2021 (hereinafter referred to as the "2020 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 (2020 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
65 473 916 (as of March 31, 2021)	62 (0.000095%)	0 (0%)	323 (0.00049%)	107 (0.00016%)	3 (0.0000046%)

* 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 Preventative 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	22	149
Female	40	174
Unknown	0	0
Total	62	323

Table 3 Number of reports by age group

Age group	Reports by MAHs		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	9	0	85	38	1
10 - 19	2	0	18	3	0
20 - 29	6	0	25	4	0
30 - 39	5	0	35	4	0
40 - 49	9	0	24	6	0
50 - 59	4	0	19	4	0
60 - 69	8	0	26	5	0
70 - 79	3	0	45	19	0
80 or older	12	0	36	17	2
Unknown	4	0	10	7	0
Total	62	0	323	107	3

(3) Details of reported symptoms

Suspected adverse reactions to influenza vaccines reported during the 2020 season are outlined by System Organ Class (SOC) in the right-hand columns of Table 4. There were no major changes compared with the 2019 season (October 1, 2019 to September 30, 2020).

A total of 3 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.

For the 1 additional case reported after the season, It was decided that the causal relationship between the vaccination and death could not be assessed due to lack of information.

A total of 13 cases (Note 1) were reported as possible Guillain-Barre syndrome or acute disseminated encephalomyelitis (ADEM) within the season. Of these, 3 cases and 1 case, respectively, were determined to be of Guillain-Barre syndrome, and of ADEM for which a causal relationship between the respective disease and the influenza vaccine was reasonably possible, according to expert opinions.

A total of 29 cases (Note 2) were reported as possible anaphylaxis. Of these, 7 cases were assessed as Level 3 or higher anaphylaxis using the Brighton Criteria (including 7 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 August, 2021, 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 terminology “Guillain-Barre syndrome” or “ADEM.”
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 2019 and 2020 seasons (by SOC)

	2019 season †		2020 season ††	
SOC of symptom	Reports by MAHs	Reports by medical institutions (serious cases)	Reports by MAHs	Reports by medical institutions (serious cases)
Gastrointestinal disorders	1	9	5	9
General disorders and administration site conditions	19	53	22	24
Infections and infestations	10	16	4	15
Haepatobiliary disorders	7	4	6	3
Eye disorders	0	1	1	2
Musculoskeletal and connective tissue disorders	5	7	4	17
Blood and lymphatic system disorders	1	7	5	5
Vascular disorders	0	3	0	5
Respiratory, thoracic and mediastinal disorders	8	14	4	2
Ear and labyrinth disorders	1	0	1	1
Injury, poisoning and procedural complications	0	4	0	1
Cardiac disorders	0	3	4	3
Nervous system disorders	28	29	16	48
Renal and urinary disorders	0	1	2	4
Psychiatric disorders	0	1	0	0
Metabolic and nutritional disorders	0	2	2	2
Endocrine disorder	0	0	5	0
Skin and subcutaneous tissue disorders	8	12	7	16
Immune system disorders	6	15	9	8
Investigations	4	2	5	2
Total	98	183	102	167

† Reported from October 1, 2019 to September 30, 2020
†† Reported from October 1, 2020 to March 31, 2021

3. Future safety measures

As detailed in the Reporting Suspected Adverse Reactions for Routine Vaccination[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 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 1-24 for the Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council (the 57th meeting) and the 2021 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (the 4th meeting) (Joint Meeting), Reports of Suspected Adverse Reactions to Influenza Vaccines
https://www.mhlw.go.jp/content/10601000/000775252.pdf (only in Japanese)

2) MHLW: Material 3-27 for the Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council (the 66th meeting) and the 2021 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (the 15th meeting) (Joint Meeting), Reports of Suspected Adverse Reactions to Influenza Vaccines
https://www.mhlw.go.jp/content/10601000/000816315.pdf (only in Japanese)

3) Partial Amendment of Reporting Suspected Adverse Reactions for Routine Vaccinations, etc. dated August 16, 2021, Joint HSB Notification No. 0816-1 and PSEHB Notification No.0816-1, 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/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>

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-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 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, 2021, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 [1] Atezolizumab (genetical recombination)

Branded name (name of company)	Tecentriq for Intravenous Infusion 840 mg, 1200 mg (Chugai Pharmaceutical Co., Ltd.)
Therapeutic category	Other antitumor agents
Indications	<Tecentriq for Intravenous Infusion 840 mg> · PD-L1-positive, hormone receptor-negative and HER2-negative inoperable or metastatic breast cancer <Tecentriq for Intravenous Infusion 1200 mg> · Unresectable, advanced or recurrent non-small cell lung cancer · Extensive-stage small cell lung cancer · Unresectable hepatocellular carcinoma

PRECAUTIONS (revised language is underlined)

[Under new instructions]

8. IMPORTANT PRECAUTIONS	<common to all indications> Hepatic impairment and sclerosing cholangitis may occur. Liver function tests should be performed prior to and periodically during administration of this drug, and patients should be carefully monitored for their conditions.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Hepatic impairment, hepatitis, sclerosing cholangitis Hepatic impairment accompanied by increased levels of AST, ALT, Al-P, γ-GTP as well as bilirubin, etc., hepatitis, and sclerosing cholangitis may occur.
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 (April 2018 to March 2021) Cases involving sclerosing cholangitis: 4 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 10 549 Japanese market launch: April 2018

<Sclerosing cholangitis> Reported in Japan (1)

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
1	Female 80s	Lung adenocarcinoma (none)	1200 mg 1 dose	**Sclerosing cholangitis** Primary disease: Lung adenocarcinoma (Stage IV) Metastasis sites: Pleura The patient's performance status (PS): 1 Prior treatment: Carboplatin, pemetrexed, bevacizumab Medical history: Cataract Day 1 of administration (Day of termination): Atezolizumab was administered as the 2nd line treatment on an inpatient basis (no further administration of atezolizumab (genetical recombination) thereafter). 7 days after administration: Upper abdominal pain developed. With no abnormal findings on ultrasound and in blood tests, the patient would be followed up. 13 days after administration: The abdominal pain did not recur. The patient was discharged from the hospital. 17 days after administration: The patient began noticing upper abdominal pain after meals and impaired appetite. 19 days after administration: The patient visited the hospital. A blood test confirmed elevated hepatobiliary enzyme levels. Cholecystitis or cholangitis was suspected from contrast CT. The patient was administered with an antibiotic and went home at her request. Drug-induced liver disorder (grade 3 at the worst) developed. [Contrast CT results] Gallbladder enlargement and bile duct wall thickness were noted, and an inflammatory change was suspected. Bile-duct stone or gallbladder tumor was not clearly identified. Biliary dilatation was mild, but biliary wall was thickened. Slight enhancement of the hepatic parenchyma was noted along the bile duct at the arterial phase. Cholangitis was suggested. Calculus or neoplastic lesions were not clearly identified. 20 days after administration: Symptoms did not improve. The patient visited the hospital again. Examination at the gastroenterological medicine department was requested from the respiratory medicine department. The patient was admitted to the respiratory medicine department for treatment assuming cholecystitis or cholangitis considering the physical conditions and laboratory test results (elevated AST, ALT, CRP, γ-GTP, ALP levels). Administration of an antibiotic was initiated. 26 days after administration: The inflammatory reaction was improving with fasting, fluid replacement, and antibiotics treatment. However, sustained elevation of hepatobiliary enzyme levels was noted. Drug-induced hepatic impairment was suspected, and examination at the gastroenterological medicine department was requested from the respiratory medicine department again. 28 days after administration: The patient was transferred to the gastroenterological medicine department. Body temperature was 36.3 °C. No abnormal abdominal physical findings were noted. Magnetic resonance cholangiopancreatography (MRCP) and liver biopsy were performed. Primary sclerosing cholangitis was suspected. Conservative therapy was performed with ursodeoxycholic acid 300 mg/day and an agent for liver disease 40 mL. The patient was monitored for 3 days with no signs of improvement seen. <MRCP results> Bile duct wall thickening and stenosis/thickening of bilateral intrahepatic bile ducts, and beaded appearance were noted. These findings did not contradict a diagnosis of primary sclerosing

					cholangitis. The localized wall thickness at the bottom of the gallbladder was accompanied by small-cystic changes suggesting adenomyoma. No abnormal findings were noted in the pancreas. <Liver biopsy results> Moderate inflammatory cell infiltration that consists of mostly lymphocytes with a few eosinophils and neutrophils was observed in the portal tract area. Cell inflammation slightly invaded part of the lobe, but hepatic cells were virtually intact except for slight adipose degeneration, with no fibrosing.
				33 days after administration	Administration of prednisolone 50 mg (1 mg/kg body weight) was initiated (for 9 days).
				36 days after administration	Day 3 of administration of prednisolone data showed no improvement in hepatobiliary enzyme levels. Administration of prednisolone continued.
				39 days after administration	A blood test confirmed slight decline of hepatobiliary enzyme, which was considered to be prednisolone responsiveness.
				41 days after administration	Hepatobiliary enzyme levels worsened. The risk of adverse reaction to prednisolone was considered to outweigh the benefits, and reduction of the drug was decided as a course of action.
				42 days after administration	The dose of prednisolone was reduced to 30 mg/day and by 5 mg/day every 5 days of administration thereafter.
				47 days after administration	Steroid responsiveness was poor. Ursodeoxycholic acid was increased to 600 mg/day, then to 900 mg/day to continue administration. No definite exacerbation of abdominal pain was noted thereafter.
				53 days after administration	MRCP was performed. <MRCP results> The intrahepatic bile ducts were poorly visualized due to motion artifact. The slight diameter irregularity in the left and right intrahepatic bile ducts was unchanged. A low-signal structure was found in the lower bile duct. The possibility for it to be biliary sludge or bile-duct stone was noted.
				54 days after administration	Administration of bezafibrate 400 mg/day was initiated.
				56 days after administration	Improvement in hepatobiliary enzyme levels was first noted around this time. Prednisolone kept being tapered.
				68 days after administration	A blood test indicated mild elevation of inflammation reaction, but hepatobiliary enzyme levels were improving. With her request granted, the patient was discharged from the hospital. A definitive diagnosis is yet to be reached, and administration of prednisolone at the maintenance dose of 10 mg/day has continued on an outpatient basis since discharge.
				81 days after administration	MRCP was performed. Hepatobiliary enzyme levels have continued to be high since then; however, there are signs of improvement. <MRCP results> Beaded irregularities of the intrahepatic bile duct were noted, slightly progressed from the previous time. No obvious abnormalities were found in the common bile duct. There were no new findings.
Concomitant drugs: Common cold drugs					

Laboratory test values

	1 day before	6 days after	9 days after	13 days after	19 days after	26 days after	27 days after	34 days after	41 days after	56 days after	134 days after
Total bilirubin (mg/dL)	0.54	0.47	0.20	0.21	0.43	0.47	0.56	0.61	1.37	1.18	1.96
AL-P (IU)	165	204	195	283	929	1 741	1 774	2 347	1 818	1 041	985
AST (IU)	26	22	23	41	86	215	186	206	181	135	60
ALT (IU)	18	12	11	28	75	168	200	315	434	355	70
γ-GTP (IU)	22	25	24	54	274	780	808	819	1 481	1 162	690
CRP (mg/dL)	-	1.57	1.66	2.36	5.50	1.77	4.76	3.12	0.86	0.72	-
LDH (IU)	-	251	230	221	261	319	275	295	285	210	-
Anti-mitochondrial antibody	-	-	-	-	-	-	<20-fold	-	-	-	-
Smooth muscle antibody	-	-	-	-	-	-	<20-fold	-	-	-	-
IgG4 (mg/dL)	-	-	-	-	-	-	27.0	-	-	-	-

<Sclerosing cholangitis> Reported in Japan (2)

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
2	Female 70s	Lung adenocarcinoma (hypertension) (hyperlipidaemia) (osteoporosis)	1200 mg/once every 3 weeks	**Sclerosing cholangitis** Primary disease: Primary lung cancer (Stage IIIA) Metastasis sites: None PS: 0. Prior treatment: 1st line; carboplatin, paclitaxel, 2nd line; pemetrexed Day 1 of administration: Administration of atezolizumab was initiated (1 200 mg/once/3 weeks). 267 days after administration (Day of termination): Administration of atezolizumab (13th course) 288 days after administration: Elevation in AST and ALT was noted in the periodic blood test. Scheduled administration of atezolizumab was canceled. Hepatitis virus and antinuclear antibody were negative. IgG4 was within the normal range. Abdominal CT and echo revealed no intrahepatic presence of mass or intrahepatic bile duct dilation. Administration of liver supporting agents was initiated assuming drug-induced liver disorder. 289 days after administration: The patient was admitted to the hospital due to nausea. Ursodeoxycholic acid and an agent for liver disease were administered with no improvement observed. 297 days after administration: The patient was discharged from the hospital. 315 days after administration: With scarce improvement seen afterwards, liver biopsy was performed. <Liver biopsy results> An ultrasound-guided needle biopsy was performed. Histopathological findings of bile biopsy confirmed ring fibrosis and inflammatory cell infiltration in the bile duct periphery. 321 days after administration: Sclerosing cholangitis was diagnosed by the pathology department. Oral administration of prednisolone 30 mg/day was initiated for the presumably immune related adverse event (irAE) induced by atezolizumab. 324 days after administration: Hepatobiliary enzyme levels showed a decline and then returned to normal. Steroid administration was continued with tapering. Sclerosing cholangitis improved.
Concomitant drugs: Atorvastatin calcium hydrate, esomeprazole magnesium hydrate, calcitriol				

Laboratory test values

	Day 1 of administration	127 days after administration	267 days after administration	288 days after administration	309 days after administration	321 days after administration	324 days after administration
Total bilirubin (mg/dL)	0.5	0.6	0.6	1.9	3.4	2.4	1.4
AL-P (IU)	285	-	-	2 837	1 955	1 404	1 145
AST (IU)	22	21	44	180	311	107	68
ALT (IU)	13	15	29	229	239	90	76
γ-GTP (IU)	12	11	78	870	464	328	306
CRP (mg/dL)	0.42	0.20	3.56	4.36	3.98	3.79	1.58
LDH (IU)	174	151	174	285	265	196	199

<Sclerosing cholangitis> Reported in Japan (3)

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
3	Female 60s	Lung adenocarcinoma (none)	1200 mg/once every 3 weeks	**Sclerosing cholangitis** Primary disease: Lung adenocarcinoma Metastasis sites: Brain PS:- Prior treatment:- Medical history: Asthma, dyslipidemia Day 1 of administration: Chemotherapy was initiated (atezolizumab + bevacizumab + paclitaxel + carboplatin) for lung adenocarcinoma in the left superior lobe and its metastasis to the brain. 66 days after administration (Day of termination): Atezolizumab (4th course) was administered. 87 days after administration: The scheduled chemotherapy was canceled considering declined PS. 106 days after administration: The patient visited the emergency department with abdominal pain and vomiting as chief complaints. Marked elevation of hepatobiliary enzyme levels were noted. Sclerosing cholangitis developed. The patient was admitted to the hospital for scrutiny and treatment. 121 days after administration: Based on the characteristic findings, such as the presence of CD8-positive lymphocytes confirmed in liver biopsy as well as the patient's medication history, sclerosing cholangitis, an irAE induced by atezolizumab, was diagnosed and steroid therapy was selected as the treatment policy. 122 days after administration: Intravenous infusion of prednisolone 50 mg/day was initiated. 136 days after administration: The dose of prednisolone intravenous infusion was reduced to 40 mg/day. 143 days after administration: Prednisolone was switched to oral preparations with the dose reduced to 30 mg/day. 145 days after administration: Sclerosing cholangitis improved, and the patient was discharged from the hospital.
	Concomitant drugs: Bevacizumab, paclitaxel, carboplatin, acetaminophen, duloxetine hydrochloride, lansoprazole, amlodipine besilate, suvorexant			

Laboratory test values

	106 days after administration	122 days after administration	127 days after administration	130 days after administration	134 days after administration	144 days after administration
AL-P (IU)	1 355	1 414	835	622	500	452
AST (IU)	176	79	24	22	19	30
ALT (IU)	125	57	34	25	25	62
γ-GTP (IU)	580	490	328	259	198	169
LDH (IU)	247	130	103	127	114	145

3
Revision of Precautions (No.328)

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 October 15, November 16, 2021.

1 Vaccines
Coronavirus modified uridine RNA vaccine (SARS-CoV-2)

Branded name	Comirnaty intramuscular injection (Pfizer Japan Inc.)
[Under New instructions]	
15. OTHER PRECAUTIONS **15.1 Information Based on Clinical Use (newly added)**	It is suggested that the frequency of myocarditis and pericarditis was higher in the male adolescents and young adults inoculated with the other coronavirus modified uridine RNA vaccine (SARS-CoV-2) by comparing the reporting rates of myocarditis and pericarditis in the domestic suspected adverse reaction reports after the start of vaccination and the estimated background incidence rates of myocarditis and pericarditis in the general population utilizing a domestic medical information database.

2 Vaccines
Coronavirus modified uridine RNA vaccine (SARS-CoV-2)

Branded name	COVID-19 Vaccine Moderna Intramuscular Injection (Takeda Pharmaceutical Company Limited.)
[Under New instructions]	
15. OTHER PRECAUTIONS **15.1 Information Based on Clinical Use (newly added)**	It is suggested that the frequency of myocarditis and pericarditis was higher in the male adolescents and young adults inoculated with this vaccine by comparing the reporting rates of myocarditis and pericarditis in the domestic suspected adverse reaction reports after the start of vaccination and the estimated background incidence rates of myocarditis and pericarditis in the general population utilizing a domestic medical information database.

3 Other antitumor agents
Atezolizumab (genetical recombination)

Branded name	Tecentriq for Intravenous Infusion 840 mg, 1200 mg (Chugai Pharmaceutical Co., Ltd.)
[Under New instructions]	
8. IMPORTANT PRECAUTIONS	<common to all indications> Hepatic impairment and sclerosing cholangitis may occur. Liver function tests should be performed prior to and periodically during administration of this drug, and patients should be carefully monitored for their conditions.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Hepatic impairment, hepatitis, sclerosing cholangitis Hepatic impairment accompanied by increased levels of AST, ALT, Al-P, γ-GTP as well as bilirubin, etc., hepatitis, and sclerosing cholangitis may occur.

4

List of Products Subject to Early Post-marketing Phase Vigilance

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

(As of 31 October 2021)
◎: Products for which EPPV was initiated after October 1, 2021

	Nonproprietary name Branded name	Name of the MAH	Date of EPPV initiate
◎	Tucidinostat Hiyasta tablets 10 mg	Huya Japan G.K.	October 20, 2021
◎	Follitropin delta (genetical recombination) Rekovelle Pen for S.C. Injection 12 μg, 36 μg, 72 μg	Ferring Pharmaceuticals Co., Ltd.	October 1, 2021
	Sotrovimab (genetical recombination) Xevudy for Intravenous Injection 500 mg	GlaxoSmithKline K.K.	September 29, 2021
	L-Lysine hydrochloride, L-arginine hydrochloride Lysakare Injection	FUJIFILM Toyama Chemical Co., Ltd.	September 29, 2021
	Lutetium (^{177}Lu) hepato Lutathera Injection	FUJIFILM Toyama Chemical Co., Ltd.	September 29, 2021
	Midazolam Midafresa Injection 0.1%	Alfresa Pharma Corporation	September 27, 2021
	Rituximab (genetical recombination) *1 Rituxan Intravenous Infusion 100 mg, 500 mg	Zenyaku Kogyo Co., Ltd.	September 27, 2021
	Sacubitril valsartan sodium hydrate*2 Entresto Tablets 100 mg, 200 mg	Novartis Pharma K.K.	September 27, 2021
	Sirolimus*3 Rapalimus Tablets 1 mg	Nobelpharma Co., Ltd.	September 27, 2021
	Ibrutinib*4 Imbruvica Capsules 140 mg	Janssen Pharmaceutical K.K.	September 27, 2021
	Secukinumab (genetical recombination) [1] Cosentyx for s.c. injection 150 mg syringe [2] Cosentyx for s.c. injection 150 mg pen [3] Cosentyx for s.c. injection 75 mg syringe	Novartis Pharma K.K.	September 27, 2021
	Dinutuximab (genetical recombination) Unituxin I.V. injection 17.5 mg/5 mL	Ohara Pharmaceutical Co., Ltd.	September 22, 2021
	Imeglimin hydrochloride	Sumitomo Dainippon	September 16

Nonproprietary name Branded name	Name of the MAH	Date of EPPV initiate
Twymeeg Tablets 500 mg	Pharma Co., Ltd.	2021
Vericiguat Verquvo tablets 2.5 mg, 5 mg, 10 mg	Bayer Yakuhin Ltd.	September 15, 2021
Fremanezumab (genetical recombination) Ajovy Syringes for S.C. Injection 225 mg	Otsuka Pharmaceutical Co., Ltd.	August 30, 2021
Givosiran sodium Givlaari Subcutaneous Injection 189 mg	Alnylam Japan K.K.	August 30, 2021
Upadacitinib hydrate[*5] Rinvoq Tablets 7.5 mg, 15 mg	AbbVie GK	August 25, 2021
Dapagliflozin propylene glycolate hydrate[*6] Forxiga 5 mg, 10 mg tablets	AstraZeneca K.K.	August 25, 2021
Selexipag[*7] Uptravi Tablets 0.2 mg, 0.4 mg	Nippon Shinyaku Co., Ltd.	August 25, 2021
Fentanyl citrate[*8] Fentos Tapes 0.5 mg, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg	Hisamitsu Pharmaceutical Co., Inc.	August 25, 2021
Upacicalcet sodium hydrate Upasita IV Injection Syringe for Dialysis 25 μg, 50 μg, 100 μg, 150 μg, 200 μg, 250 μg, 300 μg	Sanwa Kagaku Kenkyusho Co., Ltd.	August 20, 2021
Teduglutide (genetical recombination) Revestive 3.8 mg for S.C. Injection	Takeda Pharmaceutical Company Limited.	August 18, 2021
COVID-19 (SARS-CoV-2) Vaccine (recombinant chimpanzee adenovirus vector) Vaxzevria Intramuscular Injection	AstraZeneca K.K.	August 16, 2021
Erenumab (genetical recombination) Aimovig Subcutaneous injection Pens 70 mg	Amgen K.K.	August 12, 2021
Risdiplam Evrysdi Dry Syrup 60 mg	Chugai Pharmaceutical Co., Ltd.	August 12, 2021
Tazemetostat hydrobromide Tazverik tablets 200 mg	Eisai Co., Ltd.	August 16, 2021
Larotrectinib sulfate Vitrakvi oral solution 20 mg/mL	Bayer Yakuhin Ltd.	August 6, 2021
Simoctocog alfa (genetical recombination) Nuwiq For I.V. Injection 250, 500, 1000, 2000, 2500, 3000, 4000	Fujimoto Pharmaceutical Corporation	August 2, 2021
Lyophilized human alpha1-proteinase inhibitor concentrate Lynspad for Intravenous Infusion 1000 mg	Grifols Therapeutics LLC.	July 27, 2021
Casirivimab (genetical recombination), Imdevimab（genetical recombination） Ronapreve for Intravenous Infusion Set 300, 1332	Chugai Pharmaceutical Co., Ltd.	July 22, 2021
Rivaroxaban[*9] Xarelto dry syrup for pediatric 51.7 mg, 103.4 mg	Bayer Yakuhin Ltd.	July 12. 2021

Nonproprietary name Branded name	Name of the MAH	Date of EPPV initiate
Amikacin sulfate Arikayce (amikacin liposome inhalation suspension) 590 mg/8.4 mL	Insmed Incorporated.	July 7, 2021
Larotrectinib sulfate Vitrakvi capsules 25 mg, 100 mg	Bayer Yakuhin Ltd.	July 7, 2021
Osilodrostat phosphate Isturisa tablets 1 mg, 5 mg	Recordati Rare Diseases Japan KK	June 30, 2021
Incobotulinumtoxin A[*10] Xeomin 50 units/100 units/200 units for Intramuscular injection	Teijin Pharma Limited.	June 23, 2021
Pemigatinib Pemazyre Tablets 4.5 mg	Incyte Biosciences Japan G.K.	June 1, 2021
Inebilizumab (genetical recombination) Uplizna for Intravenous Infusion 100 mg	Mitsubishi Tanabe Pharma Corporation	June 1, 2021
Upadacitinib hydrate[*11] Rinvoq Tablets 7.5 mg, 15 mg	AbbVie GK	May 27, 2021
Palonosetron hydrochloride Aloxi I.V. injection 0.75 mg, Aloxi I.V. infusion bag 0.75 mg	Taiho Phamaceutical Co., Ltd.	May 27, 2021
Coronavirus modified uridine RNA vaccine (SARS-CoV-2) COVID-19 Vaccine Moderna Intramuscular Injection	Takeda Pharmaceutical Company Limited.	May 24, 2021
Ofatumumab (genetical recombination) [*12] Kesimpta for s.c. injection 20 mg pen	Novartis Pharma K.K.	May 24, 2021
Polatuzumab vedotin (genetical recombination) Polivy for Intravenous Infusion 140 mg, 30 mg	Chugai Pharmaceutical Co., Ltd.	May 19, 2021
Pabinafusp alfa (genetical recombination) Izcargo for I.V. infusion 10 mg	JCR Pharmaceuticals Co., Ltd.	May 19, 2021
Denileukin diftitox (genetical recombination) Remitoro for Intravenous Drip Infusion 300 μg	Eisai Co., Ltd.	May 19, 2021
Diclofenac etalhyaluronate sodium Joyclu 30 mg intra-articular injection	Seikagaku Corporation	May 19, 2021
Anhydrous sodium sulfate/potassium sulfate/magnesium sulfate hydrate Sulprep Combination Solution	Nihon Pharmaceutical Co., Ltd.	May 19, 2021

*1 Systemic scleroderma

*2 Hypertension

*3 Refractory lymphatic diseases (lymphangioma (lymphatic malformation), lymphangiomatosis, Gorham's disease, lymphangiectasia)

*4 Chronic graft versus host disease after haematopoietic stem cell transplantation (when steroids are not sufficiently effective)

*5 Atopic dermatitis that has not responded adequately to conventional treatments

*6 Chronic kidney disease

*7 Chronic thromboembolic pulmonary hypertension inoperable or persistent/recurrent after interventional treatment

*8 Pain relief in cancers accompanied by moderate to severe pain difficult to treat with non-opioid analgesics (limited to use as a switch from other opioid analgesics)

*9 Treatment and reduction in the risk of recurrence of venous thromboembolism

*10 Leg spasm

*11 Psoriatic arthritis in patients who have responded inadequately to conventional therapy

*12 Prevention of relapse and delaying the accumulation of physical disability in patients with relapsing-remitting multiple sclerosis and patients with active secondary progressive multiple sclerosis

*13 SARS-CoV2 pneumonia (limited to patients requiring supplemental oxygen)

<Errata, on page 14, 1. Introduction in the English version of PMDSI No.387>

Original	Revised
317 of the total 525 patients reviewed	317 of the total 526 patients reviewed