Pharmaceuticals and Medical Devices Safety Information

No. 359 December 2018

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Available information is listed here

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Register here

Published by
Ministry of Health, Labour and Welfare

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Pharmaceuticals and Medical Devices Safety Information

No. 359 December 2018

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 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
AMED	Japan Agency for Medical Research and Development
BRCA	Breast cancer susceptibility gene
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
HER	Human epidermal growth factor receptor
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
RMP	Risk management plan
PSD	Pharmaceutical Safety Division
SOC	System Organ Class

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) 2018 held on November 5, 2018, it was concluded that continuation of the ongoing cautionary measures pertaining to the occurrence of abnormal behavior following administration of oseltamivir phosphate (Tamiflu), zanamivir hydrate (Relenza), peramivir hydrate (Rapiacta), and laninamivir octanoate (Inavir) (hereinafter referred to as “influenza antiviral drugs”) in patients infected with influenza was appropriate, regardless of whether influenza antiviral drugs are administered or the specific type of drug prescribed based on the assessment of available evidence including newly gathered information. 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. 1126-1 by the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated November 26, 2018) to marketing authorization holders (MAHs) so that they will encourage healthcare providers to exercise further caution.

This section will provide an overview of adverse reactions associated with the use of influenza antiviral drugs reported during the 2017/2018 season (September 1, 2017 to August 31, 2018) 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 2018 by Japan Agency for Medical Research and Development (AMED) (Research concerning Regulatory Science related to Pharmaceuticals and Medical Devices) (Chief Researcher: Dr. Nobuhiko Okabe, Director General of Kawasaki City Health Safety Research Center) for the 2017/2018 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 and such behavior may occur regardless of whether influenza antiviral drugs are administered or the specific type of drug prescribed.

* Please refer to the following URL (MHLW website) for further details on the results of the study.
https://www.mhlw.go.jp/content/11121000/000378863.pdf (only in Japanese)

(2) Cases of abnormal behavior and patient mortalities reported

Table 1 shows the number of abnormal behaviors and patient mortalities associated with influenza antiviral drugs in the 2017/2018 season reported to PMDA based on the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices (hereinafter referred to as the “PMD Act"). The results are almost comparable to the previous season. A total of 16 patient mortalities were reported; however, causality could not be assessed due to lack of sufficient information, etc. in all cases.

Table 1 Number of abnormal behavior [Note 1] and patient mortality reports following administration of influenza antiviral drugs

	2017/2018 season (Sept. 1, 2017 to Aug. 31, 2018)			2016/2017 season (Sept. 1, 2016 to Aug. 31, 2017)		
	Number of abnormal behavior reports	Number of patient mortality reports	Number of patients treated estimated by MAH	Number of abnormal behavior reports	Number of patient mortality reports	Number of patients treated estimated by MAH
Tamiflu	38	7	Approximately 3 770 000	38	4	Approximately 3 130 000
Younger than 10 years old	14	0	Approximately 1 620 000	16	1	Approximately 1 310 000
Aged 10 to 19 years	5	2	Approximately 78 000	3	0	Approximately 100 000
“Children” [Note 2]	4	0	–	2	0	–
Relenza	3	0	Approximately 2 700 000	11	1	Approximately 1 970 000
Younger than 10 years old	1	0	Approximately 900 000	1	0	Approximately 560 000
Aged 10 to 19 years	2	0	Approximately 860 000	10	1	Approximately 720 000
Rapiacta	1	3	Approximately 320 000	0	4	Approximately 270 000
Younger than 10 years old	0	0	Approximately 30 000	0	0	Approximately 20 000
Aged 10 to 19 years	0	0	Approximately 40 000	0	0	Approximately 30 000
Inavir	4	4	Approximately 6 120 000	5	1	Approximately 4 750 000
Younger than 10 years old	0	0	Approximately 600 000	0	0	Approximately 390 000
Aged 10 to 19 years	3	1	Approximately 1 560 000	5	1	Approximately 1 380 000
Xofluza [Note 3]	2	2	Approximately 37 000	–	–	–
Younger than 10 years old	0	0	Approximately 4 000	–	–	–
Aged 10 to 19 years	2	0	Approximately 7 000	–	–	–

Note 1: Regardless of the adverse reaction name terminology used when reported, abnormal behavior includes behaviors that may lead to jumping or falling from a height such as sudden movements, attempts to bolt from the room, roaming, and wandering

Note 2: The term “children” refers to patients whose age is unknown but determined to be younger than 20 years old (excluding newborns, infants, and toddlers)

Note 3: Launched in March, 2018

3. Closing Remarks (request for survey participation)

As a result of the Subcommittee’s deliberations, it was confirmed that there were no major differences in onset trends of abnormal behavior etc. As such, regardless of whether influenza antiviral drugs are administered or the specific type of drug prescribed, the current cautionary efforts regarding the occurrence of abnormal behavior should be continued to prevent serious outcomes that may result from such behaviors appearing in conjunction with influenza infection. Healthcare providers should exercise caution regarding abnormal behavior, etc. in patients infected with influenza.

Thus, healthcare providers are encouraged to understand the objectives of this study and

participate in the accumulation of case data as requested in the Participation in Research for Nationwide Situation of Abnormal Behavior of Influenza-like-Illness Patients notification (request) (HSIB Notification No. 1126-4 and PSEHB/PSD Notification No. 1126-5 dated November 26, 2018 as well as HSIB Notification No. 1126-5 and PSEHB/PSD Notification No. 1126-6 dated November 26, 2018).

[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 2018 held on November 5, 2018
https://www.mhlw.go.jp/stf/shingi2/0000183979_00001.html (only in Japanese)

· Comprehensive measures on influenza, Winter FY 2018:
http://www.mhlw.go.jp/bunya/kenkou/influenza/index.html (only in Japanese)

· Q & A on Influenza, FY 2018:
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou01/qa.html
(only in Japanese)

2

Suspected Adverse Reactions to Influenza vaccines in the 2017 Season

1. Introduction

This section describes the status of instances of suspected adverse reactions to influenza vaccines reported from October 1, 2017 through April 30, 2018 (hereinafter referred to as the “2017 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 (2017 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 medical institutions*			Reports by MAHs (serious reports)**	
Estimated number of vaccinated persons (number of vaccinations)	Number of reports (frequency)	Number of serious cases reported (frequency)	Number of patient mortality reported	Number of serious cases reported (frequency)	Number of patient mortality reported
49 176 766 (as of April 30, 2018)	246 (0.0005%)	92 (0.0002%)	9 (0.00002%)	69 (0.0001%)	0 (0%)

*reports by medical institutions were submitted in accordance with Article 68-10 of the PMD Act.
**reports by MAHs were of cases determined to be “serious” in accordance with Article 68-10 of the PMD Act. Reports by MAHs may duplicate some cases reported by medical institutions, and duplicated cases were added up as reported by medical institutions.

(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 medical institutions	Number of reports by MAHs
Male	111	29
Female	133	35
Unknown	2	5
Total	246	69

Table 3 Number of reports by age group

	Reports by medical institutions			Reports by MAHs	
Age group	Number of reports	Number of serious cases reported	Number of patient mortalities reported	Number of serious cases reported	Number of patient mortalities reported
0 - 9	84	38	3	18	0
10 - 19	20	7	0	4	0
20 - 29	23	5	0	7	0
30 - 39	20	3	0	5	0
40 - 49	17	2	0	4	0
50 - 59	10	3	0	3	0
60 - 69	25	8	1	8	0
70 - 79	23	11	0	6	0
80 or older	24	15	5	9	0
Unknown	0	0	0	5	0
Total	246	92	9	69	0

(3) Details of reported symptoms

Suspected adverse reactions to influenza vaccines reported during the 2017 season are outlined by System Organ Class (SOC) in the rightmost column of Table 4. There were no major changes compared with the 2016 season.

There were 9 cases of post-vaccination deaths reported, of which the existence of a direct causal relationship between the vaccination and the mortality was not established for 8 cases as a result of the assessment by experts. According to the expert conclusion, in 1 case reported as death due to anaphylaxis, the existence of a causal relationship between vaccination and the mortality outcome could not be ruled out. Anaphylaxis is listed in the package insert of influenza vaccines as a clinically significant adverse reaction, and must be reported if it occurs within 4 hours of vaccination under the Suspected Adverse Reaction Reporting Criteria.

A total of 14 cases (Note 1) were reported as possible Guillain-Barre syndrome or ADEM. Of these, 1cases and 4 cases respectively were determined to be 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 19 cases (Note 2) were reported as possible anaphylaxis. Of these, 6 cases were assessed as Level 3 or higher anaphylaxis using the Brighton Criteria (all of these cases were serious).

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 July 2018, 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 “anaphylaxis,” “anaphylactic reaction,” “anaphylactic shock,” “anaphylactoid reaction,” or “anaphylactoid shock.”

Table 4 Comparison of the number of suspected adverse reaction reports between the 2016 and 2017 seasons (by SOC)

	2016 season		2017 season	
	Tetravalent influenza vaccine (seasonal trivalent and H1N1)		Tetravalent influenza vaccine (seasonal trivalent and H1N1)	
SOC of symptom	Reports by medical institutions (serious cases)	Reports by MAHs	Reports by medical institutions (serious cases)	Reports by MAHs
Blood and lymphatic system disorders	6	6	4	0
Cardiac disorders	2	1	6	1
Congenital, familial and genetic disorders	0	0	0	1
Ear and labyrinth disorders	0	0	1	0
Endocrine disorders	0	1	0	0
Eye disorders	5	1	2	2
Gastrointestinal disorders	10	5	10	6

General disorders and administration site conditions	42	34	41	31
Hepatobiliary disorders	3	3	5	9
Immune system disorders	12	5	11	4
Infections and infestations	12	13	15	12
Investigations	4	5	4	6
Metabolic and nutritional disorders	2	0	2	3
Musculoskeletal and connective tissue disorders	5	4	12	5
Nervous system disorders	31	25	32	19
Renal and urinary disorders	5	5	5	3
Respiratory, thoracic and mediastinal disorders	7	4	8	8
Skin and subcutaneous tissue disorders	7	14	11	15
Vascular disorders	2	0	0	2
Injury, poisoning and procedural complications	0	0	1	0
Psychiatric disorders	1	0	0	0
Pregnancy, puerperium and perinatal conditions	0	0	0	1
Total	156	126	170	128

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, medical institutions are urged to continue to exercise caution in the 2018 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.

[References]

1) MHLW: Distributed Material 8 for the Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council (the 36th meeting) and the 2018 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (the 5th meeting) (Joint Meeting), Reports of Suspected Adverse Reactions to Influenza Vaccines
https://www.mhlw.go.jp/content/10601000/000337161.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)
https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/dl/160831-01c.pdf
(only in Japanese)
Report form
http://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/saishin.pdf
(only in Japanese)
Entry instructions
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/dl/yobou140926-5.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
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 Preventive Vaccination Act and related rules.

<Voluntary vaccination>
Adverse reactions or infections associated with voluntary vaccinations should be reported when reporting is necessary to prevent the occurrence and spread of health hazards. Refer to the following for specific cases subject to reporting. Adverse reactions and infections of unclear association with vaccinations 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 in items (1) to (8)

3

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated November 27, 2018, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 [1] Aluminum potassium sulfate hydrate/tannic acid (with saline)

Branded name (name of company)	Zione Injection (Mitsubishi Tanabe Pharma Corporation)
Therapeutic category	Hemorrhoidal preparations
Indications	Prolapsed internal hemorrhoids

PRECAUTIONS (revised language is underlined)

Contraindications	Patients with a history of hypersensitivity to any of the ingredients contained in this product
Adverse reactions (clinically significant adverse reactions)	**Anaphylaxis:** Symptoms including decreased blood pressure, dyspnea, face oedema or flushing may occur, and cases of progression to anaphylactic shock have been reported. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

[2] Aluminum potassium sulfate hydrate/tannic acid (with analgesic agents)

Branded name (name of company)	Zione Injection/Lidocaine (Mitsubishi Tanabe Pharma Corporation)
Therapeutic category	Hemorrhoidal preparations
Indications	Prolapsed internal hemorrhoids

PRECAUTIONS (revised language is underlined)

Contraindications	Patients with a history of hypersensitivity to any of the ingredients contained in this product or to amide-type local anaesthesia agents such as lidocaine
Adverse reactions (clinically significant adverse reactions)	**Anaphylaxis:** Symptoms including decreased blood pressure, dyspnea, face oedema or flushing may occur, and cases of progression to anaphylactic shock have been reported. 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 3 years and 6 months (April 2015 to September 2018). Cases involving anaphylaxis: [1], [2] 5 (no patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: [1], [2] approximately 45 000 Launched in Japan: [1], [2] March 2005

Case summary

No.	Patient		Daily dose/Treatment duration	Adverse reactions	
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 40s	Haemorrhoids (none)	7 mL 1 day	**Anaphylactic shock**	
				1 hour and 28 minutes before administration	Butropium bromide 10 mg, and bromazepam suppository 3 mg were administered to the patient. Vital signs at initial examination were as follows: blood pressure (BP) 115/58 mm Hg, heart rate (HR) 46/min, body temperature 36.0°C.
				16 minutes before administration	Sacral epidural anaesthesia: 13 mL of lidocaine 2% was injected. Vital signs: BP 112/63 mm Hg, HR 49/min.
				At the start of administration	Aluminum potassium sulfate hydrate/tannic acid was diluted with lidocaine hydrochloride. Administration of the drug was initiated. Massage was performed after injection. The total dose was 7 mL (6 o'clock direction, 3 mL and 9 o'clock direction, 4 mL) The patient body position during administration: prone position A Sumikoshi anal retractor was used during administration
				5 minutes after administration	Aluminum potassium sulfate hydrate/tannic acid was discontinued. The patient experienced dyspnoea while 4 mL of the drug was injected in a 9 o'clock direction. Marked oedema of the eyelids, lips, and auricular developed. No stridor was noted. Queasy, vomiting, and epigastric pain occurred. SpO_2 was 91%, administration of oxygen via nasal cannula at 3 L/min was initiated. Hydrocortisone sodium succinate (100 mg), metoclopramide hydrochloride (10 mg), and hydroxyzine hydrochloride (25 mg) were administered intravenously. [Organ-specific severities of anaphylactic symptoms] [Skin and mucosal symptom] Swelling of the lips and eyelids: grade 1 (mild: partial) [Gastrointestinal symptom] Abdominal pain: grade 2 (moderate: severe abdominal pain (self-controlled)) Vomiting and diarrhoea: grade 2 (moderate: several times of vomiting and diarrhoea) [Respiratory symptom] Wheezing and dyspnoea: grade 2 (moderate: wheezing by auscultation, and mild breathing difficulties) [Cardiovascular symptom] Pulse rate and blood pressure: grade 3 (severe: blood pressure decreased) [Neurological symptom] State of consciousness: grade 2 (moderate: sleepiness, mild headache, and feeling of fear)
				9 minutes after administration	Administration of oxygen via oxygen mask at 6 L/min started. BP 72/42 mm Hg, HR 80 to 90/min, and SpO_2 94%. Etilefrine hydrochloride 1/2 ample (5 mg) was intravenously administered. Systolic blood pressure was around 70 mm Hg. Etilefrine hydrochloride 1/2 ample (5 mg) was intravenously administered. Diastolic blood pressure increased to around 90 to 100 mm Hg, and SpO_2 also increased gradually.

				1 hour and 9 minutes after administration	Chills and shivering were developed. Hydrocortisone sodium succinate (100 mg) was intravenously administered. BP 114/71 mm Hg, and HR 104/min. The patient recovered from epigastric pain. As SpO_2 reached 100%, oxygen was gradually decreased. The face oedema showed a tendency toward improvement but remained.
				2 hours and 2 minutes after administration	Administration of oxygen was no longer considered necessary and the patient returned to the hospital room. The patient was orally treated with H_2-blockers on the day, and with prednisolone (10 mg) the next morning. The face oedema remitted, and it was decided that patient could be discharged the next morning.
				1 day after administration	The patient was discharged from the hospital. Anaphylactic shock remitted.
				Date unknown	[Allergy test for lidocaine] Test methods: Skin prick test, intracutaneous reactivity test, and subcutaneous challenge test Test allergen and results: Lidocaine 1% with epinephrine: negative Lidocaine 1% without epinephrine: negative
	Concomitant medications: bromazepam, butropium bromide, lidocaine				

2 Calcitriol (injectable dosage form)

Branded name (name of company)	Rocaltrol Injection 0.5, 1 (Kyowa Hakko Kirin Co., Inc.), and the others
Therapeutic category	Vitamin A and D preparations
Indications	Secondary hyperparathyroidism in patients undergoing maintenance dialysis

PRECAUTIONS (revised language is underlined)

Adverse reactions (clinically significant adverse reactions)	**Shock, anaphylaxis:** Shock or anaphylaxis may occur. Patients should be carefully monitored. If any abnormalities such as decreased blood pressure, dyspnea, or flushing 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 3 years and 7 months (April 2015 to October 2018). Cases involving shock or anaphylaxis: 1 (no patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 46 000 Launched in Japan: June 2001

Case summary

No.	Patient		Daily dose/Treatment duration	Adverse reactions	
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Male 70s	Hypocalcaemia, secondary hyperparathyroidism (chronic kidney disease)	0.5 μg 1 day	**Anaphylactic shock**	
				6 months before administration	Administration of calcitriol (capsules) was initiated.
				3 months before administration	In order to perform aortic valve replacement surgery, administration of calcitriol (capsules) was discontinued. No allergic symptoms such as rash were found during the administration.
				Day 1 of administration	Calcitriol was administered intravenously at a dosage of 0.5 μg after hemodialysis was completed.
				10 minutes after administration	The patient developed generalised itching, flushing, and wheals.
				18 minutes after administration	BP 76/43 mm Hg, and SpO_2 91%. The patient developed abdominal pain. Administration of infusion solution, oxygen inhalation (2 L), intravenous administration of steroids, and antihistamine therapy were initiated.
				43 minutes after administration	BP 112/55 mm Hg, and SpO_2 100%. Abdominal pain disappeared, and generalised itching went into remission. The patient was transported by ambulance to a neighboring hospital and admitted for follow up. Steroids, H_2-blockers, and H_1 + H_2-blocker combination therapy were prescribed for 3 days.
				1 day after administration	The patient was discharged from the hospital.
				2 months after administration	The patient was still undergoing hemodialysis.

3 Freeze-dried live attenuated varicella vaccine

Branded name (name of company)	Varicella Vaccine Live Attenuated “Biken” (The Research Foundation for Microbial Diseases of Osaka University)
Therapeutic category	Vaccines
Indications	Prevention of varicella and herpes zoster in patients aged 50 years and older

PRECAUTIONS (revised language is underlined)

Adverse reactions (clinically significant adverse reactions)	**Aseptic meningitis**: Nuchal rigidity, pyrexia, headache, nausea/vomiting, clouding of consciousness, etc. may occur. If any abnormalities are observed, appropriate measures should be taken. Cases of aseptic meningitis associated with herpes zoster have been reported even years after vaccination with this drug.
Reference information	Number of adverse reactions (for which a causal relationship with the product could not be ruled out) reported in approximately the previous 3 years and 7 months (April 2015 to October 2018). Cases involving aseptic meningitis: 1 (no patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: approximately 2 130 000 Launched in Japan: March 1987

Case summary

No.	Patient		Daily dose/Treatment duration	Adverse reactions	
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures	
1	Female under 10 years old	Varicella immunization (none)	0.5 mL 2 times	**Herpes zoster and aseptic meningitis**	
				Day of vaccination	The patient received the initial vaccination of freeze-dried live attenuated varicella vaccine at clinic A
				6 months after vaccination	The patient received the second vaccination of freeze-dried live attenuated varicella vaccine at clinic A
				3 years and 6 months after vaccination	The patient experienced a pricking pain in the thoracic region of the back.
				1 day after development of symptoms	The patient developed blisters on the left upper arm and the left chest. The patient visited the dermatology department at Hospital B, and was diagnosed with herpes zoster. Aciclovir ointment was applied. Ketotifen fumarate was prescribed for itching.
				3 days after development of symptoms	The patient experienced vomiting at night on one occasion.
				4 days after development of symptoms	The patient visited the pediatrics department at Hospital C. Aciclovir was orally administered but resulted in vomiting. Domperidone was administered via suppository to address nausea. The patient subsequently developed pyrexia.
				5 days after development of symptoms	The patient experienced vomiting again, and visited Hospital D. A cerebrospinal fluid test showed a lymphocyte predominant cell count increase. The patient was admitted to the hospital and was diagnosed with aseptic meningitis. Aciclovir was administered intravenously. Vidarabine was also administered. Pyrexia subsequently resolved.
				9 days after development of symptoms	Vomiting disappeared
				10 days after development of symptoms	All blisters became scabs.
				12 days after development of symptoms	The patient was discharged from the hospital. Intravenous aciclovir was switched to oral administration.
				19 days after development of symptoms	Administration of aciclovir was completed. Varicella virus DNA was not identified by PCR analysis of the cerebrospinal fluid sample collected 5 days after symptom onset. However, varicella virus DNA derived from the varicella vaccine strain was detected in scabs and fluid present in blisters collected 7-9 days after symptom onset.
	Suspected concomitant medications: none Concomitant medications: none				

4

Revision of Precautions (No. 299)

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 November 27, 2018.

1 Hemorrhoidal preparations

Aluminum potassium sulfate hydrate/tannic acid (with saline)

Branded name	Zione Injection (Mitsubishi Tanabe Pharma Corporation)
Contraindications	Patients with a history of hypersensitivity to any of the ingredients contained in this product
Adverse reactions (clinically significant adverse reactions)	**Anaphylaxis:** Symptoms including decreased blood pressure, dyspnea, face oedema or flushing may occur, and cases of progression to anaphylactic shock have been reported. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

2 Hemorrhoidal preparations

Aluminum potassium sulfate hydrate/tannic acid (with analgesic agents)

Branded name	Zione Injection/Lidocaine (Mitsubishi Tanabe Pharma Corporation)
Contraindications	Patients with a history of hypersensitivity to any of the ingredients contained in this product or to amide-type local anaesthesia agents such as lidocaine
Adverse reactions (clinically significant adverse reactions)	**Anaphylaxis:** Symptoms including decreased blood pressure, dyspnea, face oedema or flushing may occur, and cases of progression to anaphylactic shock have been reported. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.

3 **Vitamin A and D preparations**

Calcitriol (injectable dosage form)

Branded name	Rocaltrol Injection 0.5, 1 (Kyowa Hakko Kirin Co., Inc.), and the others
Adverse reactions (clinically significant adverse reactions)	**Shock, anaphylaxis:** Shock or anaphylaxis may occur. Patients should be carefully monitored. If any abnormalities such as decreased blood pressure, dyspnea, or flushing are observed, administration of this drug should be discontinued and appropriate measures should be taken.

4 **Vaccines**

Freeze-dried live attenuated varicella vaccine

Branded name	Varicella Vaccine Live Attenuated “Biken” (The Research Foundation for Microbial Diseases of Osaka University)
Adverse reactions (clinically significant adverse reactions)	**Aseptic meningitis:** Nuchal rigidity, pyrexia, headache, nausea/vomiting, clouding of consciousness, etc. may occur. If any abnormalities are observed, appropriate measures should be taken. Cases of aseptic meningitis associated with herpes zoster have been reported even years after vaccination with this drug.

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 ADR 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 November 30, 2018)
◎: Products for which EPPV was initiated after November 1, 2018

	Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
◎	Abemaciclib Verzenio Tablets 50 mg, 100 mg, 150 mg	Eli Lilly Japan K.K.	November 30, 2018
◎	Macrogol 4000/sodium chloride/sodium bicarbonate/potassium chloride Movicol Combination Powder	EA Pharma Co., Ltd.	November 29, 2018
◎	Omidenepag isopropyl Eybelis Ophthalmic Solution 0.002%	Santen Pharmaceutical Co., Ltd.	November 27, 2018
◎	Vibegron Beova Tablets 50 mg	Kyorin Pharmaceutical Co.,Ltd.	November 27, 2018
◎	Blinatumomab (genetical recombination) Blincyto I.V. Infusion 35 μg	Amgen Astellas BiPharma K.K.	November 27, 2018
◎	Lorlatinib Lorbrena Tablets 25 mg, 100 mg	Pfizer Japan Inc.	November 20, 2018
◎	Icatibant acetate Firazyr subcutaneous injection 30 mg syringe	Shire Japan KK	November 20, 2018
◎	Vedolizumab (genetical recombination) Entyvio for I.V. Infusion 300 mg	Takeda Pharmaceutical Company Limited.	November 7, 2018
◎	Nonacog beta pegol (genetical recombination) Refixia I.V. Injection 500, 1000, 2000	Novo Nordisk Pharma Ltd.	November 1, 2018
	Levonorgestrel/ethinylestradiol Jemina Tablets	Nobelpharma Co., Ltd.	October 4, 2018
	Spiramycin Spiramycin 1.5M IU Tablets [Sanofi]	Sanofi K.K.	September 25, 2018
	Rilpivirine hydrochloride/emtricitabine/tenofovir alafenamide fumarate Odefsey Combination Tablets	Janssen Pharmaceutical K.K.	September 20, 2018
	Fidaxomicin Dafclir Tablets 200 mg	Astellas Pharma Inc.	September 18, 2018
	Obinutuzumab (genetical recombination) Gazyva Intravenous Infusion 1000 mg	Chugai Pharmaceutical Co., Ltd.	August 29, 2018

Nonproprietary name Branded name on	Name of the MAH	Date of EPPV initiate
Durvalumab (genetical recombination) Imfinzi Injection 120 mg, 500 mg	AstraZeneca K.K.	August 29, 2018
Ipilimumab (genetical recombination) *1 Yervoy Injection 50 mg	Bristol-Myers Squibb K.K.	August 21, 2018
Nivolumab (genetical recombination) *2 Opdivo I.V. Infusion 20 mg, 100 mg, 240 mg	Ono Pharmaceutical Co., Ltd.	August 21, 2018
Tedizolid phosphate Sivextro Tablets 200 mg, Sivextro for iv infusion 200 mg	Bayer Yakuhin, Ltd.	August 21, 2018
Condoliase Hernicore 1.25 Units for Intradiscal Inj.	Seikagaku Corporation	August 1, 2018
Fosravuconazole L-lysine ethanolate Nailin Capsules 100 mg	Sato Pharmaceutical Co., Ltd.	July 27, 2018
Canakinumab (genetical recombination) *3 Ilaris for S.C. Injection 150 mg, Ilaris Solution for S.C. Injection 150 mg	Novartis Pharma K.K.	July 2, 2018
Olaparib*4 Lynparza Tablets 100 mg, 150 mg	AstraZeneca K.K.	July 2, 2018
Japanese cedar pollen extract Cedarcure Japanese Cedar Pollen Sublingual Tablets 2,000 JAU, 5,000 JAU	Torii Pharmaceutical Co., Ltd.	June 29, 2018
Ibuprofen L-lysine Ibulief I.V. Injection 20 mg	Senju Pharmaceutical Co., Ltd.	June 14, 2018
Rasagiline mesilate Azilect Tablets 0.5 mg, 1 mg	Takeda Pharmaceutical Company Limited.	June 11, 2018
Sirolimus Rapalimus Gel 0.2%	Nobelpharma Co., Ltd.	June 6, 2018
Pemafibrate Parmodia Tab. 0.1 mg	Kowa Company, Ltd.	June 1, 2018

*1 Radically unresectable or metastatic renal cell carcinoma

*2 Radically unresectable or metastatic renal cell carcinoma

*3 Systemic-onset juvenile idiopathic arthritis that does not adequately respond to existing treatments

*4 Unresectable or recurrent germline *BRCA*-mutated, HER2-negative metastatic breast cancer previously treated with chemotherapy