Pharmaceuticals and Medical Devices Safety Information

No. 329 January 2016

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on 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

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Pharmaceuticals and Medical Devices Safety Information

No. 329 January 2016

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 reaction 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 reaction, 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

ADR	Adverse drug reaction
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
BAT	Basophil activation test
BUN	Blood urea nitrogen
Cr	Creatinine
DLST	Drug-induced lymphocyte stimulation test
EPPV	Early post-marketing phase vigilance
HSB	Health Service Bureau
HSIB	Health Services and Infections Bureau
IgE	Immunoglobulin E
JIMGA	Japan Industrial and Medical Gases Association
LOT	Long-term oxygen therapy
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
PEHB	Pharmaceutical and Environmental Health Bureau
PFSB	Pharmaceutical and Food Safety Bureau
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
SD	Safety Division
SOC	System Organ Class
SpO_2	Oxygen saturation

1

Adverse Reaction to Influenza Vaccines in the 2014 Season

1. Introduction

This section presents adverse reaction to influenza vaccines reported from October 1, 2014 through June 30, 2015 (hereinafter referred to as the "2014 season").

If a condition is diagnosed as an adverse reaction falling under the Reporting Criteria for adverse reaction to influenza vaccines at a medical institution, this will be reported from the medical institution to the Ministry of Health, Labour and Wealth (MHLW) regardless of causality. Data on adverse reaction reported by medical institutions are collected and evaluated by Pharmaceuticals and Medical Devices Agency (PMDA) together with those reported by marketing authorization holders (MAHs). In serious cases including fatal cases, the causalities are also evaluated based on evidence including opinions from experts, and the necessity of safety measures is discussed.

These adverse reaction reports are investigated and reviewed on a regular basis at the joint meeting of the Adverse Reaction Review Committee for Preventative/Voluntary Vaccination in the Health Sciences 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") to discuss the necessity of safety measures[1].

2. Reports of adverse reaction to influenza vaccines (2014 season)

(1) Number of reported adverse reaction and reporting frequency

Table 1 shows the number of reported adverse reaction to the influenza vaccines and the reporting frequency calculated from the estimated number of vaccinated persons based on the amount of vaccines distributed to medical institutions.

Table 1 Number of reported adverse reaction and estimated number of vaccinated persons

	Adverse reaction reported by medical institutions			Adverse reaction reported by MAHs (serious adverse reaction reports)*	
Estimated number of vaccinated persons (number of vaccinations)	Total number of reported adverse reaction (reporting frequency)	Number of reported serious cases (reporting frequency)	Number of reported deaths	Number of reported serious cases (reporting frequency)	Number of reported deaths
52 378 967 (as of June 30, 2015)	244 (0.0005%)	99 (0.0002%)	11 (0.00002%)	63 (0.0001%)	5 (0.00001%)

*The adverse reaction reported by MAHs were determined to be "serious" in accordance with the Pharmaceutical Affairs Act Article 77-4-2 and Article 68-10 regarding ensuring quality, efficacy, and safety of pharmaceuticals and medical devices, and may duplicate with some cases of adverse reaction reports by medical institutions. Duplicate reports were added up as reports by medical institutions.

(2) Reported adverse reaction by gender and age group

The number of reported adverse reaction to influenza vaccines by gender and age group is shown in **Table 2** and **3**, respectively.

Table 2 Number of reports by gender

Gender	Number of adverse reaction reported by medical institutions	Number of adverse reaction reported by MAHs
Male	110	27
Female	133	34
Unknown	1	2
Total	244	63

Table 3 Number of reports by age group

Age	Adverse reaction reported by medical institutions			Adverse reaction reported by MAHs	
	Total number of reported adverse reaction	Number of reported serious cases		Number of reported serious cases	
			Number of reported deaths		Number of reported deaths
0-9 years	76	39	3	17	0
10-19 years	16	1	0	6	0
20-29 years	15	6	0	2	0
30-39 years	14	2	0	7	0
40-49 years	21	6	1	4	0
50-59 years	15	6	0	3	0
60-69 years	21	5	0	3	1
70-79 years	41	18	2	12	2
80 years or older	25	16	5	7	1
Unknown	0	0	0	2	1
Total	244	99	11	63	5

(3) Details of reported adverse reaction

Adverse reaction to influenza vaccines reported for the 2014 season are outlined by System Organ Class (SOC) in the right column of **Table 4**. No marked difference was noted in comparison with the reports for the 2013 season.

There were 16 cases of post-vaccination deaths reported, of which 15 cases were assessed by experts and the cases were highly likely due to exacerbation of an underlying disease or other factors. Therefore, a direct and clear causal relationship between the vaccination and the fatalities was not established.

A total of 24 cases of adverse reaction [Note 1] were reported as possible Guillain-Barre syndrome or acute disseminated encephalomyelitis. Of these, 5 cases were determined to be Guillain-Barre syndrome and acute disseminated encephalomyelitis respectively, and a causal relationship between the respective disease and the influenza vaccine could not be ruled out based on evidence including expert opinions.

A total of 28 cases of adverse reaction [Note 2] were reported as possible anaphylaxis. Of these, 10 cases were assessed as Level 3 or higher anaphylaxis using the Brighton Criteria (6 of these cases were serious).

Regarding the number of reports from MAHs by manufacturing lot, there were no specific lots in which anaphylaxis was reported more often than in other lots.

At the Joint Meeting held in November 2015, it was determined that there were no new concerns regarding safety of vaccines, including other adverse reaction, and it was decided that taking actions such as revision of package inserts would not be necessary at present but continuous caution will be paid to the status of adverse reaction reports and its details.

Note 1: Includes cases reported using adverse reaction terms such as numbness, feeling of weakness, neuropathy, muscular weakness, and difficulty swallowing.
Note 2: Cases reported as “anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock”.

Table 4 Comparison of the number of adverse reaction reports between the 2013 and 2014 season (by SOC)

	2013 season*		2014 season**	
	Trivalent influenza vaccine (seasonal bivalent and H1N1)		Trivalent influenza vaccine (seasonal bivalent and H1N1)	
SOC of adverse reaction*	Reports by medical institutions (serious reports)	Reports by MAHs	Reports by medical institutions (serious reports)	Reports by MAHs
Blood and lymphatic system disorder	11	2	3	3
Cardiac disorders	4	1	2	0
Ear and labyrinth disorders	1	1	0	0
Eye disorders	2	1	0	2
Gastrointestinal disorders	6	0	3	5
General disorders and administration site conditions	21	24	28	27
Hepatobiliary disorders	6	3	4	1
Immune system disorders	9	5	15	6
Infections and infestations	11	7	15	8
Investigations	2	3	2	8
Metabolism and nutrition disorders	0	0	0	2
Musculoskeletal and connective tissue disorders	14	3	7	6
Nervous system disorders	32	16	30	12
Renal and urinary disorders	4	9	5	3
Respiratory, thoracic, and mediastinal disorders	8	1	13	5
Skin and subcutaneous tissue disorders	9	17	13	14
Pregnancy, puerperium, and perinatal conditions	1	0	0	0
Vascular disorders	0	2	3	1
Injury, poisoning, and procedural complications	0	0	1	0
Psychiatric disorders	1	2	0	0
Social circumstances	0	0	1	0
Total	142	97	145	103

*Adverse reaction terms were coded in accordance with the Medical Dictionary for Regulatory Activities/J Ver. 17.0
**Adverse reaction terms were coded in accordance with the Medical Dictionary for Regulatory Activities/J Ver. 18.0

3. Future safety measures

As detailed in "Reporting Adverse Reaction for Routine Vaccination"[2], medical institutions are encouraged to promptly report any adverse reaction considered to meet the Adverse Reaction Reporting Criteria even if the causality is unclear.

In addition, medical institutions are requested to continue to exercise caution in the 2015 season for the following issues concerning anaphylaxis:

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

MHLW/PMDA will continue to gather safety information of influenza vaccines including adverse reaction reports and to adopt safety measures.

<References>

1 MHLW: Distributed Material 9 for the Adverse Reaction Review Committee for Preventative/Voluntary Vaccination in the Health Sciences Council (the 16th meeting) and the 2015 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (the 6th meeting) (the Joint Meeting), Report of Adverse Reaction to Influenza Vaccines
http://www.mhlw.go.jp/file/05-Shingikai-10601000-Daijinkanboukouseikagakuka-Kouseikagakuka/0000105680.pdf
(Only available in Japanese language)

2 Reporting Adverse Reaction for Routine Vaccination: Health Service Bureau (HSB) Notification No. 0330-3 and Pharmaceutical and Food Safety Bureau (PFSB) Notification No. 033-1, by the Director-General of HSB and PFSB, dated March 30, 2013 (partially amended July 16, 2014 and September 26, 2014)
http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/kekkaku-kansenshou/yobou-sesshu/
(Only available in Japanese language)
Report form:
http://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/saisin.pdf
(Only available in Japanese language)
Description guideline: http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/dl/yobou140926-5.pdf
(Only available in Japanese language)

Reference: Adverse Reaction Reporting Criteria
<Routine vaccination>

Anaphylaxis	4 hours
Hepatic function disorder	28 days
Interstitial pneumonia	28 days
Acute disseminated encephalomyelitis	28 days
Guillain-Barre syndrome	28 days
Convulsion	7 days
Vasculitis	28 days
Thrombocytopenic purpura	28 days
Asthmatic attack	24 hours
Nephrotic syndrome	28 days
Encephalitis or encephalopathy	28 days
Oculomucocutaneous syndrome	28 days
Other symptoms considered to be strongly associated with the vaccination by the physician and requiring hospital admission, resulting in death or physical disability, or possibly resulting in death or physical disability	Time frame in which the event was considered to be strongly associated with the vaccination by the physician

Except for “other reaction”, any event occurring within the specific time frame is subject to mandatory reporting to the MHLW regardless of causality according to the Preventative Vaccination Law and associated related rules.

<Voluntary vaccination>

Adverse reaction or infections associated with voluntary vaccinations should be reported when reporting is necessary to prevent the occurrence or spread of health hazards. Refer to the following for specific cases subject to reporting. Adverse reaction 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) Requiring admission or prolonged hospitalization at medical institutions for treatment [excluding events in (3) and (4)]
(6) Serious events corresponding to those in (1) to (5)
(7) Congenital disease or anomaly 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 (1) to (8)

2

Safety of Influenza Antiviral Drugs

1. Introduction

The 2015 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council held a 5th meeting on November 6, 2015 and determined that caution should continue to be exercised in regards to occurrence of abnormal behavior after administration of oseltamivir phosphate (Tamiflu), zanamivir hydrate (Relenza), peramivir hydrate (Rapiacta), and laninamivir octanoate hydrate (Inavir) (hereinafter referred to as "influenza antiviral drugs") based on assessment of available evidence including newly gathered information. Based on this decision, the MHLW has issued notifications regarding "Calling attention to the Precautions in the Package Insert of Influenza Antiviral Drugs" [Pharmaceutical and Environmental Health Bureau (PEHB)/Safety Division (SD) Notification No. 1118-1 to 1118-5 dated November 18, 2015] to MAHs so that they will encourage healthcare professionals to exercise caution.

This section will provide an overview of the adverse reaction related to influenza antiviral drugs reported for the 2014/2015 season (September 1, 2014 to August 31, 2015) during the aforementioned meeting.

2. Reports of abnormal behavior, etc.

(1) Research on abnormal behavior associated with influenza infection

Study results for the "Research on abnormal behavior during influenza-like infections" commissioned by the MHLW Sciences Research Grant (Chief Researcher: Director Nobuhiko Okabe, Kawasaki City Health Safety Research Center) for the 2014/2015 season were reported, and results related to occurrence of severe abnormal behavior were relatively similar to previous reports. Based on these results, it was confirmed that such behavior occurs regardless of whether influenza antiviral drugs are used or not and regardless of the type of influenza antiviral drug prescribed.

*Please refer to the following URL (MHLW homepage) for further details on the results of the research.
http://www.mhlw.go.jp/file/05-Shingikai-11121000-Iyakushokuhinkyoku-Soumuka/0000103556.pdf
(Only available in Japanese language)

(2) Reports on fatal cases and abnormal behavior

Table 1 shows the number of abnormal behavior and fatal cases associated to influenza antiviral drugs reported in the 2014/2015 season to the PMDA based on the Pharmaceuticals and Medical Devices Act. The results are almost comparable to the previous season. A total of 8 fatal cases were reported; however, a causal relationship between the products and the fatal outcome could not be assessed due to lack of information, etc.

Table 1 Number of abnormal behavior [Note 1] reports and fatal cases after administration of influenza antiviral drugs

	2014/2015 season (Sept. 1, 2014 to Aug. 31, 2015)			2013/2014 season (Sept. 1, 2013 to Aug. 31, 2014)		
	Number of abnormal behavior reports	Number of fatal cases	Number of patients using these drugs estimated by MAH	Number of abnormal behavior reports	Number of fatal cases	Number of patients using these drugs estimated by MAH
Tamiflu	24	5	Approximately 2 880 000	23	7	Approximately 2 850 000
Of which, are younger than 10 years old	14	0	Approximately 1 140 000	15	1	Approximately 1 290 000
Of which, are in their 10s	2	0	Approximately 70 000	1	0	Approximately 130 000
Of which, are "pediatric" [Note 2]	2	0	-	1	0	-
Relenza	3	0	Approximately 1 370 000	5	1	Approximately 1 460 000
Of which, are younger than 10 years old	0	0	Approximately 280 000	0	1	Approximately 250 000
Of which, are in their 10s	3	0	Approximately 650 000	4	0	Approximately 690 000
Rapiacta	0	2	Approximately 210 000	1	0	Approximately 240 000
Of which, are younger than 10 years old	0	0	Approximately 20 000	0	0	Approximately 20 000
Of which, are in their 10s	0	0	Approximately 30 000	1	0	Approximately 30 000
Inavir	5	1	Approximately 3 800 000	10	3	Approximately 3 310 000
Of which, are younger than 10 years old	0	0	Approximately 380 000	2	0	Approximately 330 000
Of which, are in their 10s	3	0	Approximately 1 060 000	6	0	Approximately 910 000

Note 1: Regardless of the adverse reaction term used, abnormal behavior includes behavior that may lead to jumping or falling from a height such as sudden running, trying to escape from the room, roaming around, and wandering.

Note 2: "Pediatrics" refers to cases whose age is unknown but determined to be younger than 20 years old (excludes newborns, infants, and toddlers).

3. Closing comments (Request for participation in study)

Based on the deliberation results of the Subcommittee, there were no major differences in onset trends of abnormal behavior, etc. As such, regardless of whether influenza antiviral drugs are used or not and regardless of the type of influenza antiviral drug prescribed, continuous encouragement to exercise caution for abnormal behavior is considered necessary in order to prevent occurrence of serious outcomes due to abnormal behavior associated with influenza infection.

Healthcare professionals should exercise caution for abnormal behavior, etc. during influenza infections.

Furthermore, research on abnormal behavior during influenza-like infections will be continued this year as well. Thus, healthcare professionals are encouraged to understand the objectives of this research and participate in gathering case information as requested in the "(Request for) Participation in Research on Abnormal Behavior During Influenza-like Infections" (Health Services and Infections Bureau (HSIB) Notification No. 1120-5 and PEHB/SD Notification No. 1120-1 dated November 20, 2015 as well as HSIB Notification No. 1120-6 and PEHB/SD Notification No. 1120-2 dated the same day).

[References]

- Materials from the 2015 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (5th meeting):
  http://www.mhlw.go.jp/stf/shingi2/0000103565.html
  (Only available in Japanese language)
- Influenza Q&A 2015:
  http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou01/qa.html
  (Only available in Japanese language)

2 Administration in patients with a history of hypersensitivity to milk products

Cases of anaphylaxis have been reported among patients with hypersensitivity to milk products being treated with laninamivir octanoate hydrate and zanamivir hydrate, which are influenza antiviral drugs, in Japan. Based on this evidence, the MHLW/PMDA instructed MAHs to revise the Precautions section of the package insert of these products on August 6, 2015 for the purpose of alerting caution when administering these products to applicable patients. The details of the revision were introduced in the Pharmaceuticals and Medical Devices Safety Information (PMDSI) No. 326 (dated September 2015). However, the details of the revision including case summaries that served as the basis for these revisions will be introduced in this section once again since it is now influenza season and opportunities for prescribing these drugs have increased.

Active ingredient	(1) Laninamivir octanoate hydrate (2) Zanamivir hydrate
Brand name (name of company)	(1) Inavir Dry Powder Inhalers 20 mg (Daiichi Sankyo Company, Limited) (2) Relenza (GlaxoSmithKline K.K.)
Therapeutic category	Antivirals
Indications	(1) and (2) Treatment and prophylaxis of influenza A or B virus infections

PRECAUTIONS (underlined parts are revised)

Careful administration: Patients with a history of hypersensitivity to milk products

Important precautions: This drug uses lactose hydrate which contains milk proteins. There have been reports of anaphylaxis upon administration of this drug to patients with a history of hypersensitivity to milk products. Therefore, caution should be exercised when administering this drug to such patients.

Case summary: Laninamivir octanoate hydrate

No.	Patient		Daily dose/ Treatment duration	Adverse reaction
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female Less than 10 years old	Influenza (Food allergy, asthma bronchial, dermatitis atopic)	20 mg for 1 day	**Anaphylaxis and bronchospasm** The patient had a history of various food allergies such as milk and eggs. 2 days before administration: The patient suffered from pyrexia and mild coughing since the afternoon. Day 1 of administration: There were no problems with the patient's consciousness level. The patient consulted a medical

institution due to persistent pyrexia, coughing, and nasal discharge. Tests for influenza B came back positive.
The patient started coughing and wheezing after inhaling laninamivir octanoate hydrate at the dispensing pharmacy. The patient consulted the medical institution again due to itchiness of the eye, continued coughing, and dyspnoea.
18 minutes after inhalation:
Confirmed nasal alar breathing, retractive breathing, and marked asthma. Oxygen saturation (SpO_2) was 88%. The patient had ocular hyperaemia, swelling of eyelids, and slight facial redness, and was slumping in her mother's arms. The patient remained alert. Inhalation of 5 L oxygen, sodium cromoglicate, and salbutamol sulfate.
20 minutes after inhalation:
Blood pressure was 128/67. Dyspnoea persisted and the patient was wheezing and had moist rales.
25 minutes after inhalation:
Intramuscularly administered adrenaline 0.2 mL. Rapidly resolving wheezing, and completely resolved dyspnoea such as retractive breathing.
35 minutes after inhalation:
SpO_2 was 97% (R/A). Wheezing and rales remained but were gradually resolving. Watchful waiting after secure blood vessels.
70 minutes after inhalation:
Conditions resolved and the patient was able to drink water.
135 minutes after inhalation:
Mild wheezing (+). Admitted to a different hospital for observation.
2 days after administration:
The patient was discharged from the hospital.

Laboratory examination

Prick test, Drug induced lymphocyte stimulation test (DLST), Allergen (drug) specific basophil activation test (BAT)

	Prick test	DLST	BAT
This drug	Positive	Negative	Positive
Lactose hydrate	Positive	Negative	Positive
Laninamivir octanoate hydrate	Negative	Negative	Negative
Active metabolite	Negative	-	-

IgE tests

	Approximately 2 months before administration	Approximately 2 months after administration	Approximately 5 months after administration
Total IgE (IU/mL)	551	824	678
Milk (UA/mL)	46.80	97.60	66.60

Concomitant medications: montelukast sodium, epinastine hydrochloride, fluticasone propionate

Case summary: Zanamivir hydrate

No.	Patient		Daily dose/ Treatment duration	Adverse reaction
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male Less than 10 years old	Influenza B (Asthma, attention deficit/hyperactivity disorder, dermatitis atopic, rhinitis allergic)	20 mg for 1 day	**Anaphylactic shock, diarrhoea, difficulty breathing (dyspnoea), flushed face, dehydration, nausea, vomiting, pyrexia, and cough.** The patient had a history of egg allergy, milk allergy, and anaphylactic shock due to milk. Day 1 of administration: The patient was diagnosed as influenza B. Treatment with zanamivir hydrate 10 mg twice daily was started. Acetaminophen 200 mg was administered concomitantly. 1 day after administration (Day of discontinuation): Onset of diarrhoea. Treatment with zanamivir hydrate was discontinued. 1 day after discontinuation: The patient consulted a nearby clinic in the morning. Facial expressions were rigid, and, although the patient did not have cyanosis, his body temperature was 37.7°C. The patient had difficulty breathing, flushed face, and coughs. Usually, the patient is very talkative, but he was unable to answer questions. Blood pressure was within normal range, SpO_2 was 90%, and pulse was 97. The patient was suspected to be in anaphylactic shock. Confirmed nausea and vomiting. The patient was administered adrenaline 0.2 mg intramuscularly and hydrocortisone sodium succinate 100 mg + glucose 5% (500) + sodium chloride 20 mL, after which he was emergently transported to a hospital. After being transported, the patient was administered sodium chloride 250 mL loaded 100 mL/h due to dehydration, after which maintenance fluid was continued at 20 mL/h. The patient was admitted to the hospital for observation. Salbutamol sulfate/bromhexine hydrochloride 3 times per day was administered for the treatment of influenza. Breathing difficulty and flushed face were resolving. 2 days after discontinuation: Other symptoms were also resolving. The patient was discharged from the hospital since there was no pyrexia or anaphylactic symptoms. However, consulted the emergency outpatient ward in the evening due to pyrexia. General conditions were good; thus, the patient was prescribed ephedra decoction 2.5 g twice daily, carbocisteine 0.4 g + ambroxol hydrochloride 0.4 g 3 times a day, and tolubuterol tape 1 mg, and sent home. 4 days after discontinuation: The patient consulted a nearby clinic. Conditions resolved to normal, and no abnormalities were observed.
	Laboratory examination [1 day after discontinuation] Cr 0.44 mg/dL, Total IgE 2207 IU/mL, BUN 25.7 mg/dL Albumen: 48.60 UA/mL (Reference value: 0.03-0.34), Milk: 84.00 UA/mL (Reference value: 0.03-0.34), alpha-lactoglobulin: 14.50 UA/mL (Reference value: 0.03-0.34), beta-lactoglobulin:			

	12.80 UA/mL (Reference value: 0.03-0.34), casein: 73.00, Other allergens for which the patient tested positive: household dust, ticks, cats, dogs, cedar, Japanese cypress, yolk, and ovomucoid.
	Co-suspect drug: acetaminophen Concomitant medications: montelukast sodium, ketotifen fumarate, budesonide, sodium cromoglicate

3

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated November 24, 2015, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Lenvatinib mesilate

Brand name (name of company)	Lenvima Capsules 4 mg and 10 mg (Eisai Co., Ltd.)
Therapeutic category	Antineoplastics - Miscellaneous
Indications	Radically unresectable thyroid cancer

PRECAUTIONS (underlined parts are revised)

Careful administration	Patients with tumour invasion in the carotid arteries, veins, etc.
Important precautions	Carotid artery exposure, carotid artery haemorrhage, and tumour haemorrhage associated with tumour shrinkage or necrosis may occur during administration of this drug. Furthermore, there were case reports of development of massive bleeding from exposed carotid artery sites or fistula formulation sites. There is a risk of haemoptysis or haematemesis in a patient with a tracheal fistula or oesophageal fistula. Caution should be exercised before administration of this drug by confirming tumour invasion in the carotid arteries, veins, etc. During administration of this drug, patients should be carefully monitored, and fully carried out to confirm the presence or absence of fistula formation. If any haemorrhage are observed, administration of this drug should be discontinued as necessary, and appropriate measures should be adopted. Furthermore, particular caution should be exercised for anaplastic thyroid cancer patients as many of these patients suffer from tumour invasion in the carotid arteries, veins, etc.
Adverse reaction (clinically significant adverse reaction)	**Haemorrhage:** Haemorrhage such as epistaxis, haematuria, haemoptysis, gingival bleeding, pulmonary haemorrhage, rectal haemorrhage, intracranial tumour haemorrhage, arterial haemorrhage, subarachnoid haemorrhage, cerebral haemorrhage, and gastrointestinal haemorrhage may occur. In addition, carotid artery haemorrhage and tumour haemorrhage associated with tumour shrinkage or necrosis may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as dose reduction or drug suspension should be adopted. If severe haemorrhage occurs, administration of this drug should be discontinued, and appropriate measures should be adopted.
Reference information	The number of reported adverse reaction (for which a causality to the drug could not be ruled out) for the past 6 months (from initial marketing to October 2015). Cases of adverse reaction associated with carotid artery exposure, carotid artery haemorrhage, and tumour haemorrhage associated with tumour shrinkage or necrosis: 5 cases (no fatal case) The number of patients using this drug estimated by the MAH: Approximately 493 (from initial marketing to October 2015) Launched in Japan: May 2015

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/ Treatment duration</th><th>Adverse reaction</th></tr>
<tr><th>Sex/ Age</th><th>Reason for use (complications)</th><th>Clinical course and therapeutic measures</th></tr>
<tr><td>1</td><td>Female 60s</td><td>Anaplastic thyroid cancer (Unknown)</td><td>24 mg for 16 days
↓
Rest period
↓
20 mg for 16 days</td><td>Arterial haemorrhage
The patient’s history is unknown.
Day 1 of administration:
The diameter of the tumour (maximum diameter) was 43 mm. The tumour invasion was seen in the carotid artery and skin. Because the tumour had relapsed in the skin, deep invasion was unclear. Administration of lenvatinib mesilate 24 mg was started (the patient was admitted to the hospital for treatment implementation).
Day 13 of administration:
The patient was discharged from the hospital.
Day 17 of administration:
Aspartate aminotransferase / Alanine aminotransferase (ALT) increased. Administration of lenvatinib mesilate was suspended due to proteinuria.
Day 22 of administration:
Dosage of lenvatinib mesilate was decreased to 20 mg and administration of the drug was restarted.
Day 35 of administration:
The diameter of the tumour was 0 mm.
Day 38 of administration (Day of discontinuation):
Slight, gradual haemorrhaging was observed from the morning, and the patient conducted astriction on her own. Afterwards, the patient was admitted to the hospital at night since arresting the haemorrhage became difficult. Astriction was applied. Administration of lenvatinib mesilate was suspended.
1 day after discontinuation:
Excessive haemorrhage from the right common carotid artery occurred early in the morning and the haemorrhage could not be controlled.
The patient underwent emergency surgery (i.e. right common carotid artery ligation). The haemorrhage was resolving.</td></tr>
<tr><td></td><td colspan="4">Laboratory examination
<table>
<tr><th></th><th>6 days before administration</th><th>Day 3 of administration</th><th>Day 24 of administration</th><th>1 day after discontinuation</th><th>5 days after discontinuation</th></tr>
<tr><td>Platelet count (×10^4/mm^3)</td><td>24.3</td><td>21.2</td><td>13.1</td><td>11.3</td><td>14.7</td></tr>
<tr><td>International normalized ratio</td><td>-</td><td>0.85</td><td>-</td><td>1.21</td><td>0.95</td></tr>
<tr><td>Prothrombin time (sec.)</td><td>-</td><td>10.8</td><td>-</td><td>14.4</td><td>11.3</td></tr>
<tr><td>Activated partial thromboplastin time (sec.)</td><td>-</td><td>27.3</td><td>-</td><td>84.0</td><td>32.6</td></tr>
</table></td></tr>
<tr><td></td><td colspan="4">Concomitant medications: unknown</td></tr>
</table>

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reaction
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 60s	Anaplastic thyroid cancer (Unknown)	24 mg for 8 days	**Arterial haemorrhage** The patient's history is unknown. 1 day before administration: The diameter of the tumour before administration of lenvatinib mesilate was 80 mm. Tumour invasion was seen in the skin, oesophagus, and trachea. Complete invasion of the skin, and suspected invasion of the oesophagus and trachea. Invasion of the blood vessels was not seen on the echo. Day 1 of administration: Administration of lenvatinib mesilate 24 mg was started (the patient was admitted to the hospital for treatment implementation). Day 6 of administration: Tumour became necrotic and deciduate. Skin fistula developed in the area where the tumor became deciduate (i.e. neck), and exudate oozed out even though blood vessels were not exposed. The fistula was covered with a gauze, and the exudate was wiped off. There was no haemorrhage at this point. Day 8 of administration (Day of discontinuation): Haemorrhage occurred near the carotid artery, and the patient pressed the emergency call button herself. Lost consciousness and went into cardiac arrest 2 minutes later. Common carotid artery ligation was conducted by a vascular surgeon, and the patient was moved to the Intensive Care Unit and managed on an artificial respirator. Administration of lenvatinib mesilate was discontinued. 2 days after discontinuation: The patient was removed from the artificial respirator and recovered spontaneous respiration, and was thereby moved back to the hospital ward. 38 days after discontinuation: The tumor enlarged, and the patient died due to exacerbation of the primary disease.
	Laboratory examination Unknown			
	Concomitant medications: unknown			

4

Revision of Precautions (No. 270)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated November 24 and November 26, 2015.

1 Antidotes

Fomepizole

Brand name	Fomepizole Intravenous Infusions 1.5 g “TAKEDA” (Takeda Pharmaceutical Co., Ltd.)
Adverse reaction (clinically significant adverse reaction)	**Anaphylaxis**: Anaphylaxis may occur. Patients should be carefully monitored. If abnormalities such as dyspnoea, wheezing, and flushing are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.

2 Antineoplastics - Miscellaneous

Nivolumab (genetical recombination)

Brand name	Opdivo Intravenous Infusions 20 mg and 100 mg (Ono Pharmaceutical Co., Ltd.)
Adverse reaction (clinically significant adverse reaction)	**Type 1 diabetes mellitus**: Type 1 diabetes mellitus (including fulminant type 1 diabetes mellitus) may occur and cause diabetic ketoacidosis. Patients should be carefully monitored for symptoms such as thirst, nausea, and vomiting or increase in blood glucose levels. If type 1 diabetes mellitus is suspected, administration of this drug should be discontinued, and appropriate measures such as administration of insulin products should be adopted.

3 Antivirals

Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate

Brand name	Stribild Combination Tablets (Japan Tobacco Inc.)
Contraindications	Patients being administered the following drugs: carbamazepine, phenobarbital, phenytoin, fosphenytoin, rifampicin, food containing hypericum perforatum (St. John’s Wort), dihydroergotamine mesilate, ergotamine tartrate, ergometrine maleate, methylergometrine maleate, asunaprevir, vaniprevir, simvastatin, pimozide, sildenafil citrate, vardenafil hydrochloride hydrate, tadalafil, blonanserin, azelnidipine, rivaroxaban, triazolam, midazolam.

Interactions (contraindications for concomitant use)	Carbamazepine, phenobarbital, phenytoin, fosphenytoin, rifampicin, food containing hypericum perforatum (St. John's Wort)
Precautions for concomitant use	~~Carbamazepine, phenobarbital, phenytoin~~ (deleted)

4 **Antivirals**

Ombitasvir hydrate/paritaprevir hydrate/ritonavir

Brand name	Viekirax Combination Tablets (AbbVie G.K.)
Contraindications	Patients with moderate or severe hepatic function disorder (Child–Pugh Class B or C)
Important Precautions	Hepatic function disorder may occur. Periodic liver function tests should be performed during treatment. Hepatic function disorder is more likely to be observed within 4 weeks after the start of administration. Hepatic function should be assessed more frequently at the early stage after starting administration, as needed. Regardless of the increase in hepatic enzyme levels, blood bilirubin level may significantly increase, and hepatic failure may be observed along with ascites, hepatic encephalopathy etc. Patients should be carefully monitored. If any signs of liver failure are observed, appropriate measures should be adopted after the discontinuation of administration.
Adverse reaction (clinically significant adverse reaction)	**Hepatic function disorder, hepatic failure**: Hepatic function disorder associated with elevated ALT (GPT)* and/or bilirubin** levels etc. may occur. In addition, regardless of the hepatic enzyme increase, blood bilirubin levels may increase significantly, and the disorder may result in hepatic failure associated with ascites, hepatic encephalopathy etc. If there are any signs of an abnormality in hepatic function, the patient should be carefully monitored with more frequent laboratory tests. If worsening of symptoms is observed, appropriate measures should be adopted such as discontinuation of the administration. If the ALT (GPT) level persistently exceeds 10 times the upper limit of the standard value, or if any signs of hepatic failure are observed, administration of this drug should be discontinued and appropriate measures should be adopted. * More than 5 times the upper limit of the standard level, ** More than 3 times the upper limit of the standard level

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 new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its MAH is responsible for collecting the adverse drug reaction (ADR) from all of the medical institutions where the drugs are used and taking safety measures. The aim of the EPPV is to promote the rational proper use of drugs in medical treatments, and to promptly take actions for prevention of the serious ADR. EPPV is specified as a condition of approval.

(As of November 30, 2015)
◎: Products for which EPPV was initiated after November 1, 2015

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	sucroferric oxyhydroxide P-TOL Chewable Tablets 250 mg, 500 mg	Kissei Pharmaceutical Co., Ltd.	November 27, 2015
◎	ombitasvir hydrate/paritaprevir hydrate/ritonavir Viekirax Combination Tablets	AbbVie G.K.	November 26, 2015
◎	glatiramer acetate Copaxone S.C. Injections 20 mg Syringe	Takeda Pharmaceutical Co., Ltd.	November 26, 2015
◎	vildagliptin/metformin hydrochloride EquMet Combination Tablets LD and HD	Novartis Pharma K.K.	November 26, 2015
◎	Omarigliptin Marizev Tablets 12.5 mg, 25 mg	MSD K.K.	November 26, 2015
◎	None Actair House Dust Mite Sublingual Tablets 100 units (IR) and 300 units (IR)	Shionogi & Co., Ltd.	November 19, 2015
	Ciprofloxacin Ciproxan I.V. 200 mg[*1]	Bayer Yakuhin, Ltd.	September 24, 2015
	Lamotrigine Lamictal Tablets for Pediatric Use 2 mg, 5 mg, Lamictal Tablets 25 mg, 100 mg[*2]	GlaxoSmithKline K.K.	September 24, 2015
	Rivaroxaban Xarelto Tablets 10 mg, 15 mg[*3]	Bayer Yakuhin, Ltd.	September 24, 2015
	olanexidine gluconate (1) Olanedine Antiseptic Solution 1.5% (2) Olanedine Solution 1.5% Antiseptic Applicator 10 mL (3) Olanedine Solution 1.5% Antiseptic Applicator 25 mL	Otsuka Pharmaceutical Co., Ltd.	September 16, 2015
	dulaglutide (genetical recombination) Trulicity Ateos Subcutaneous Injection 0.75 mg	Eli Lilly Japan K.K.	September 16, 2015

Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
collagenase (clostridium histolyticum) Xiaflex Injection	Asahi Kasei Pharma Corporation	September 16, 2015
antithrombin gamma (genetical recombination) Acoalan Injection 600	Kyowa Hakko Kirin Co., Ltd.	September 7, 2015
hydroxychloroquine sulfate Plaquenil Tablets 200 mg	Sanofi K.K.	September 7, 2015
insulin glargine (genetical recombination) Lantus XR Injection SoloStar	Sanofi K.K.	September 7, 2015
ledipasvir acetonate/sofosbuvir Harvoni Combination Tablets	Gilead Sciences, Inc.	September 1, 2015
talaporfin sodium Laserphyrin 100 mg Injection[*4]	Meiji Seika Pharma Co., Ltd.	September 1, 2015
eliglustat tartrate Cerdelga Capsule 100 mg	Genzyme Japan K.K.	September 1, 2015
nintedanib ethanesulfonate Ofev Capsules 100 mg, 150 mg	Nippon Boehringer Ingelheim Co., Ltd.	August 31, 2015
panobinostat lactate Farydak Capsules 10 mg, 15 mg	Novartis Pharma K.K.	August 31, 2015
ipilimumab (genetical recombination) Yeryov Injection 50 mg	Bristol-Myers K.K.	August 31, 2015
asfotase alfa (genetical recombination) Strensiq Subcutaneous Injection 12 mg/0.3 mL, 18 mg/0.45 mL, 28 mg/0.7 mL, 40 mg/1 mL, 80 mg/0.8 mL	Alexion Pharma G.K.	August 31, 2015
catridecacog (genetical recombination) NovoThirteen Intravenous Injections 2 500	Novo Nordisk Pharma Ltd.	August 27, 2015
nitric oxide INOflo for Inhalation 800 ppm[*5]	Air Water Inc.	August 24, 2015
bosentan hydrate Tracleer Tablets 62.5 mg[*6]	Actelion Pharmaceuticals Japan Ltd.	August 24, 2015
ribavirin Rebetol Capsules 200 mg[*7]	MSD K.K.	July 29, 2015
clindamycin phosphate hydrate/benzoyl peroxide Duac Combination Gel	GlaxoSmithKline K.K.	July 17, 2015
gadobutrol Gadovist IV Injection 1.0 mol/L Syringe 5 mL, 1.0 mol/L Syringe 7.5 mL, 1.0 mol/L Syringe 10mL	Bayer Yakuhin, Ltd.	June 30, 2015
bortezomib Velcade Injection 3 mg[*8]	Janssen Pharmaceutical K.K.	June 26, 2015
lidocaine/propitocaine EMLA Cream[*9]	Sato Pharmaceutical Co., Ltd.	June 26, 2015
edaravone Radicut Injection 30 mg, Radicut Bag for I.V. Infusion 30 mg[*10]	Mitsubishi Tanabe Pharma Corporation	June 26, 2015
botulinum toxin type A Botox for Injection 50 units, 100 units[*11]	GlaxoSmithKline K.K.	June 26, 2015

Nonproprietary name Brand name on		Name of the MAH	Date of EPPV initiate
	tazobactam/piperacillin hydrate	Taiho Pharmaceutical Co., Ltd.	June 26, 2015
	Zosyn IV Injection 2.25 and 4.5, Zosyn Fixed-dose Bag for I.V. Infusion 4.5*12		
	pitavastatin calcium hydrate	Kowa Company, Ltd.	June 26, 2015
	Livalo Tablets 1 mg and 2 mg, Livalo OD Tablets 1 mg and 2 mg*13		
	ramucirumab (genetical recombination)	Eli Lilly Japan K.K.	June 22, 2015
	Cyramza Injection 100 mg, 500 mg		
	Macitentan	Actelion Pharmaceuticals Japan Ltd.	June 9, 2015
	Opsumit Tablets 10 mg		
	tramadol hydrochloride	Nippon Shinyaku Co., Ltd.	June 2, 2015
	Onetram Tablets 100 mg		

*1 Pediatric indication and dosage
*2 Typical absence seizures
*3 Treat deep-vein thrombosis (DVT) and pulmonary embolism, and prevent DVT and pulmonary embolism from relapse
*4 Localized, residual recurrent esophageal carcinoma after chemoradiotherapy or radiotherapy
*5 Improvement of pulmonary hypertension in the perioperative period of cardiac surgery
*6 Suppress development of digital ulcers in systemic sclerosis (scleroderma)
*7 Improvement of viremia in patients with serogroup 2 chronic hepatitis C or compensated cirrhosis type C in combination therapy with sofosbuvir
*8 Mantle cell lymphoma
*9 Pediatric dose for pain relief during skin laser therapy and indications for pain relief during pricking injection of an intravenous indwelling needle
*10 Suppress progression of functional disorders associated to amyotrophic lateral sclerosis (ALS)
*11 Strabismus
*12 Febrile neutropenia (new pediatric dose)
*13 Familial hypercholesterolemia (new pediatric dose)

(Reference)

Precautions Regarding Handling of Fire during Long-Term Oxygen Therapy (LOT)

1. Introduction

Long-term oxygen therapy (LOT) is an at-home treatment for chronic respiratory failure patients to inhale highly-concentrated oxygen by using an oxygen concentrator, liquid oxygen units, and oxygen cylinders (hereinafter referred to as an "oxygen concentrator").

The oxygen concentrator can be used safely when properly used in accordance with the instructions in the package insert and the user's manual. Since oxygen is a combustion-enhancing gas, however, sources of fire should be handled with the utmost care. The package insert and the user's manual contain precautions not to put any sources of fire close to the oxygen concentrator. Moreover, the MHLW and the Japan Industrial and Medical Gases Association (JIMGA) have prepared and distributed leaflets and videos for handling of fire during LOT to alert patients and their families.

However, fatal fire accidents believed to be caused by smoking, etc. have still occurred repeatedly in patients using LOT. Accordingly, healthcare professionals, patients, and their families are advised again to take thorough precautions.

Table 1 shows Cases of serious health damage due to fire in the houses of patients using LOT for which information was updated as of the end of November 2014 by the JIMGA.

2. Request for taking thorough safety measures

As the MHLW and the JIMGA have issued an alert against fire accidents, patients using LOT and their families need to take the following precautions against handling of fire when using the oxygen concentrator. Healthcare professionals are advised again to thoroughly alert patients and their families.

(1) Sources of fire, including smoking near an oxygen concentrator while using LOT, may cause items such as cannulas and clothing to ignite, resulting in severe burn injuries or house fires.

(2) Any sources of fire should not be put within 2 meters of an oxygen concentrator. Smoking is strictly prohibited especially while using LOT.

(3) Oxygen will not cause items such as cannulas and clothing to ignite or cause home fires when properly used in accordance with the user's manual and appropriate precautions against fire. You are advised to use oxygen therapy in accordance with the instructions given by the doctor without being unduly afraid.

<References>

1. MHLW: Precautions Regarding Handling of Fire During LOT
   http://www.mhlw.go.jp/stf/houdou/2r98520000003m15_1.html
   (Only available in Japanese language)
2. Cases of serious health damage due to fire in the houses of patients using LOT (JIMGA)
   http://www2.jimga.or.jp/dl/iryo/all/top/HOT_jiko.pdf
   (Only available in Japanese language)
3. Precautions against Handling of Fire during LOT (JIMGA)
   http://www.jimga.or.jp/front/bin/ptlist.phtml?Category=7041
   (Only available in Japanese language)

Table 1 Cases of serious health damage due to fire in the houses of patients using LOT (Prepared by JIMGA [as of the end of November, 2015])

No	Date of Issue	Prefecture	Age (Gender)	Damage	Cause (Including assumptions)
1-19	December 2003 – December 2007			18 deaths, 1 serious injury	Smoking, electrical leak, stoves, etc.
20	March 2008	Yamaguchi	70s (Female)	Death	Smoking
21	November 2008	Tokyo	70s (Male)	Death	Lighted incense with lighter
22	January 2009	Nara	90s (Male)	Death (death by fire)	Stove
23	February 2009	Kagoshima	50s (Male)	Death (death by fire)	Smoking
24	March 2009	Chiba	80s (Male)	Death (death by fire)	Stove or Buddhist alter
25	May 2009	Saitama	70s (Female)	Death (death by fire)	(Unknown: near an electrical tap)
26	October 2009	Kyoto	80s (Male)	Death (death by fire)	Smoking
27	November 2009	Hyogo	60s (Female)	Death (death by fire)	(Unknown)
28	December 2009	Tokyo	70s (Male)	Serious injury (burns) ➔ death	(Unknown)
29	January 2010	Osaka	80s (Male)	Serious injury (burns) ➔ death	Smoking
30	September 2010	Kanagawa	60s (Male)	Death (death by fire)	(Unknown: possibly careless handling of cigarettes)
31	September 2010	Tokyo	70s (Male)	Death (death by fire)	(Unknown: was not a smoker)
32	November 2010	Tokushima	80s (Male)	Death (death by fire)	(Unknown)
33	January 2011	Osaka	40s (Female)	Death	(Unknown: possibly smoking)
34	January 2011	Hyogo	80s (Male)	Death (death by fire)	(Unknown)

35	April 2011	Nagano	70s (Female)	Death (death by fire)	Careless handling of cigarettes
36	April 2011	Okayama	60s (Male)	Death (death by fire)	Careless handling of cigarettes
37	September 2011	Wakayama	70s (Male)	Death (death by fire)	(Unknown: possibly candles)
38	June 2012	Okayama	80s (Male)	Death	Smoking
39	November 2012	Kyoto	70s (Female)	Death (death by fire)	(Unknown: possibly stove)
40	November 2012	Osaka	60s (Male)	Death (death by fire)	(Unknown: possibly smoking)
41	March 2013	Fukuoka	80s (Male)	Death (death by fire)	(Unknown)
42	August 2013	Okinawa	70s (Male)	Serious injury (burns in the airway)	(Unknown)
43	November 2013	Niigata	80s (Female)	Death (death by fire)	(Unknown: possibly stove)
44	November 2013	Yamagata	70s (Male)	Death (death by fire)	(Unknown)
45	December 2013	Osaka	80s (Female)	Death	(Unknown)
46	January 2014	Saitama	80s (Male)	Death (death by fire)	Electrical leak
47	January 2014	Gifu	60s (Female)	Death (death by fire)	Electrical leak
48	January 2014	Akita	70s (Male)	Death (death by fire)	(Unknown: possibly stove)
49	April 2014	Nagano	70s (Male)	Death	(Unknown)
50	May 2014	Aichi	70s (Male)	Death (death by fire)	(Unknown)
51	August 2014	Osaka	80s (Female)	Death	Smoking
52	October 2014	Tokyo	70s (Male)	Death	Smoking
53	February 2015	Osaka	80s (Male)	Death (death by fire)	(Unknown)
54	April 2015	Chiba	80s (Female)	Death	(Unknown)
55	May 2015	Saitama	60s (Male)	Death (death by fire)	(Unknown)
56	June 2015	Shizuoka	70s (Female)	Burns over the entire body (serious injury)	(Unknown)
57	November 2015	Aichi	80s (Male)	Death	(Unknown: possibly extension cords)