Pharmaceuticals and Medical Devices Safety Information

No. 349 December 2017

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Pharmaceuticals and Medical Devices Safety Information

No. 349 December 2017

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 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
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CK-MB	Creatine kinase MB
CRP	C-reactive protein
CT	Computed tomography
ECG	Electrocardiogram
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
HSB	Health Service Bureau
HSIB	Health Services and Infections Bureau
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
MR	Magnetic resonance
MRI	Magnetic resonance imaging
PFSB	Pharmaceutical and Food Safety Bureau
PMD Act	Act on Securing Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices
PMDA	Pharmaceuticals and Medical Devices Agency
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
PV Law	Preventative Vaccination Law
SD	Safety Division
SOC	System organ class

1

Safety of Influenza Antiviral Drugs

1. Introduction

The 2017 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council held the 8th Fiscal Year (FY) 2017 meeting on November 9, 2017 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 (Inavir) (hereinafter referred to as "influenza antiviral drugs") based on assessment of available evidence including newly gathered information, irrespective of use or the type of influenza antiviral drugs. Moreover, deaths from falls considered to be related to abnormal behavior continue to be reported, and the necessity of providing a specific explanation when calling attention to the risk was pointed out. Based on this opinion, Ministry of Health, Labour and Welfare (MHLW) has issued a notification regarding "Calling further attention to the Precautions of influenza antiviral drugs" [PSEHB/ SD Notifications No. 1127-3 to 1127-7 dated November 29, 2017] to marketing authorization holders (MAHs) so that they will encourage healthcare providers to exercise further caution, and at the same time, the description of abnormal behavior in the "Q & A on Influenza, FY 2017" of the MHLW website page on "Comprehensive measures on influenza Winter FY 2017" has been revised.

< Specific measures >

General principles ***Current precautions**

- If a child or adolescent has influenza, he or she should not be left alone for at least 2 days after starting treatment, regardless of the type of influenza antiviral drug prescribed or of whether such a drug has been used or not.

Additional measures to keep children and adolescents from dashing out outdoors (Example)

*** Newly added measures (Example)**

(1) For a high-rise residence

- Lock the front door and windows in all rooms (including using internal locks or auxiliary locks, if available)
- Have the child sleep in a room that is not facing a balcony
- Have the child sleep in a room that has a latticed window (if there is such as room)

(2) For an independent housing

- In addition to (1), have the child sleep on the ground floor, if possible

This section will provide an overview of the adverse reaction related to influenza antiviral drugs reported for the 2016/2017 season (September 1, 2016 to August 31, 2017) during the aforementioned meeting.

2. Reports of abnormal behavior

(1) Research on abnormal behavior associated with influenza infection

Study results for the “Research for Nationwide Situation of Abnormal Behavior of Influenza-like-Illness Patients” commissioned in FY 2017 by Japan Agency for Medical Research and Development (Research on Regulatory Science of Pharmaceuticals and Medical Devices) (Chief Researcher: Dr. Nobuhiko Okabe, Director General of Kawasaki City Health Safety Research Center) for the 2016/2017 season were reported. Based on these results, it was confirmed that occurrence of severe abnormal behavior was relatively similar to previous reports and such behavior occurs regardless of whether influenza antiviral drugs are used or not, or of the type of the influenza antiviral drugs prescribed.

* Please refer to the following URL (MHLW website) for further details on the results of the research.

http://www.mhlw.go.jp/file/05-Shingikai-11121000-Iyakushokuhinkyoku-Soumuka/0000184039.pdf
(Only available in Japanese language)

(2) Reports on abnormal behavior and fatal cases

Table 1 shows the number of abnormal behaviors and fatal cases associated with influenza antiviral drugs in the 2016/2017 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 10 fatal cases were reported; however, a causal relationship between the drugs and the fatal outcome could not be assessed due to lack of information etc. in all cases

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

	2016/2017 season (Sept. 1, 2016 to Aug. 31, 2017)			2015/2016 season (Sept. 1, 2015 to Aug. 31 2016)		
	Number of abnormal behavior reports	Number of fatal cases	Number of patients treated estimated by MAH	Number of abnormal behavior reports	Number of fatal cases	Number of patients treated estimated by MAH
Tamiflu	38	4	Approximately 3 130 000	25	1	Approximately 3 050 000
Of which, those younger than 10 years old	16	1	Approximately 1 310 000	17	0	Approximately 1 470 000
Of which, those aged 10 to 19 years	3	0	Approximately 100 000	0	0	Approximately 85 000
Of which, those that are “pediatric” [Note 2]	2	0	-	1	0	-
Relenza	11	1	Approximately 1 970 000	4	1	Approximately 2 550 000
Of which, those younger than 10 years old	1	0	Approximately 560 000	0	0	Approximately 1 010 000
Of which, those aged 10 to 19 years	10	1	Approximately 720 000	2	1	Approximately 810 000
Rapiacta	0	4	Approximately 270 000	0	3	Approximately 290 000
Of which, those younger than 10 years old	0	0	Approximately 20 000	0	0	Approximately 30 000
Of which, those aged 10 to 19 years	0	0	Approximately 30 000	0	0	Approximately 40 000
Inavir	5	1	Approximately 4 750 000	11	2	Approximately 3 920 000
Of which, those younger than 10 years old	0	0	Approximately 390 000	0	0	Approximately 470 000
Of which, those aged 10 to 19 years	5	1	Approximately 1 380 000	8	0	Approximately 1 050 000

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

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

3. Closing comments (Request for participation in survey)

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, or of the type of influenza antiviral drugs prescribed, continuous encouragement to exercise caution for abnormal behavior is considered necessary in order to prevent the occurrence of serious outcomes due to abnormal behavior associated with influenza infection. Healthcare providers should exercise caution regarding abnormal behavior etc. during influenza infections.

Furthermore, research for nationwide situation of abnormal behavior of influenza-like-illness patients is being continued this year as well. Thus, healthcare providers are encouraged to understand the objectives of this research and participate in gathering case information as requested in the "(Request for) Participation in Research for Nationwide Situation of Abnormal Behavior of Influenza-like-Illness Patients" (HSIB Notification No. 1127-2 and PSEHB/SD Notification No. 1127-1 dated November 27, 2017 as well as HSIB Notification No. 1127-3 and PSEHB/SD Notification No. 1127-2 dated the same day).

[Reference]

- Documentations form the 2017 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (8th meeting):
  http://www.mhlw.go.jp/stf/shingi2/0000183979.html
  (Only available in Japanese language)
- Comprehensive measures on influenza Winter FY 2017:
  http://www.mhlw.go.jp/bunya/kenkou/influenza/index.html
  (Only available in Japanese language)
- Q & A on Influenza, FY 2017:
  http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou01/qa.html
  (Only available in Japanese language)

Q.10: What should I do if I get influenza?

(1) If you do not feel well, get yourself examined at a medical institution early on.
(2) Stay quiet and rest. It is particularly important to get plenty of sleep.
(3) Drink plenty of water to rehydrate. Any sort of liquids you prefer, such as tea or soup, would be fine.
(4) If you have symptoms such as cough or sneezing, wear a nonwoven fabric mask so that you will not infect those around you.
(5) Avoid going out into crowds or downtown areas, and do not force yourself to go to school or work if you are not up to it.

When children or adolescents have influenza, there is a risk of abnormal behavior such as sudden running, trying to bolt from a room, or wandering. If you are caring for a child or adolescent at home, you will need to keep an eye on him or her and not leave him or her alone for at least 2 days after influenza has been diagnosed and treatment has begun (See Q15).

Q.14: I heard that abnormal behavior, including death from falls, has been reported after taking influenza antiviral drugs, but were the drugs the cause of it?

Abnormal behavior (examples: Sudden running, trying to bolt from a room, or wandering) has been reported after taking influenza antiviral drugs. Moreover, death from falls, etc., has been reported to have occurred as a result of such abnormal behavior, although these cases have been extremely rare.

* 8 such cases from April 2009 onward (as of August 31, 2017)

It is unknown whether taking influenza antiviral drugs was the cause of the abnormal behavior, but investigation results thus far report:

- In patients who have influenza, similar abnormal behavior may be observed even if they have not taken any medicines;
- The abnormal behavior may occur regardless of the type of influenza antiviral drug prescribed.

Based on these findings, it is necessary to take precautions against abnormal behavior regardless of the type of influenza antiviral drug prescribed or of whether an influenza antiviral drug was used or not (Refer to Q15 for specific precautions).

Q.15: What should we watch out for in order to prevent falls or other accidents due to abnormal behavior?

Abnormal behavior has been reported in patients who have influenza, regardless of the type of influenza antiviral drug prescribed or of whether an influenza antiviral drug was used or not (Refer to Q14).

As a general rule, if you are caring for a child or adolescent with influenza at home, a guardian or other adult will need to keep an eye on the patient and not leave him alone for at least 2 days after influenza has been diagnosed and treatment has begun, regardless of the type of anti-influenza drug prescribed or of whether an anti-influenza drug was used or not.

In addition, even if abnormal behavior has occurred, measures such as the following can be taken to keep the child or adolescent from easily dashing outside.

(1) For a high-rise residence

- Lock the front door and windows in all rooms (including using internal locks or auxiliary locks, if available)
- Have the child sleep in a room that is not facing a balcony
- Have the child sleep in a room that has a latticed window (if there is such a room)

(2) For an independent housing

- In addition to (1), have the child sleep on the ground floor, if possible

< Examples of abnormal behavior >

- Suddenly standing up and trying to get out of a room
- Becoming excited, running around a room with outstretched hands, and saying things that make no sense
- Getting excited, opening a window, and trying to get out onto a balcony
- Leaving a residence, walking outside, and not responding when spoken to
- Rushing outside with the sense of being attacked by others
- Saying strange things and moving about a room while crying
- Suddenly laughing and trying to run up stairs

Reports of abnormal behavior “when taking influenza antiviral drugs”

(Since compilation of report in June of 2009)

< Method of aggregation >

According to the PMD Act, MAHs (pharmaceutical companies) are obligated to report to the Minister of Health, Labour and Welfare any cases of adverse reactions associated with the drugs that they handle and that have come to their attention (adverse reaction report). The following totals were made by summarizing adverse reaction reports for each season.

Adverse reaction reports include cases for which a causal relationship to the drug is unknown. The causal relationship between influenza antiviral drugs and abnormal behavior is considered unknown.

	2009/2010 season		2010/2011 season		2011/2012 season		2012/2013 season	
	Number of abnormal behavior reports		Number of abnormal behavior reports		Number of abnormal behavior reports		Number of abnormal behavior reports	
	Total	Fatal case	Total	Fatal case	Total	Fatal case	Total	Fatal case
Tamiflu	50	1	16	0	31	0	31	0
Of which, adolescents	44	0	15	0	20	0	19	0
Relenza	65	0	8	1	7	0	1	0
Of which, adolescents	62	0	8	1	7	0	1	0
Rapiacta	Unapproved.	Unapproved	1	0	4	0	3	0
Of which, adolescents	-	-	1	0	3	0	0	0
Inavir	Unapproved.	Unapproved.	5	0	15	1	2	0
Of which, adolescents	-	-	4	0	15	1	1	0

	2013/2014 season		2014/2015 season		2015/2016 season		2016/2017 season		Total	
	Number of abnormal behavior reports		Number of abnormal behavior reports		Number of abnormal behavior reports		Number of abnormal behavior reports		Number of abnormal behavior reports	
	Total	Fatal case	Total	Fatal case	Total	Fatal case	Total	Fatal case	Total	Fatal case
Tamiflu	23	2	24	0	25	0	38	0	238	3
Of which, adolescents	17	0	16	0	18	0	21	0	170	0
Relenza	5	0	3	0	4	1	11	1	104	3
Of which, adolescents	4	0	3	0	2	1	11	1	98	3
Rapiacta	1	0	0	0	0	0	0	0	9	0
Of which, adolescents	1	0	0	0	0	0	0	0	5	0
Inavir	10	0	5	0	11	0	5	1	53	2
Of which, adolescents	8	0	3	0	8	0	5	1	44	2

(Note) Numbers reported in documents at council meetings are aggregated by season. Total counts of abnormal behavior may differ slightly from the number of cases when similar aggregation is performed at the present time because of withdrawal of reports or reports of additional symptoms after aggregation for each season. The tabulation period differs slightly for each season.

< Tabulation period for each season >

2009/2010 season, April 2009 to June 2010; 2010/2011 season, July 2010 to September 2011,
2011/2012 season, October 2011 to August 2012; 2012/2013 season, September 2012 to August 2013
2013/2014 season, September 2013 to August 2014; 2014/2015 season, September 2014 to August 2015
2015/2016 season, September 2015 to August 2016; 2016/2017 season, September 2016 to August 2017

Reports of abnormal behavior in influenza patients

(2015/2016 season, 2016/2017 season)

< Survey method >

In “Research for Nationwide Situation of Abnormal Behavior of Influenza-like-Illness Patients”[1] (Chief Researcher: Dr. Nobuhiko Okabe, Director General of Kawasaki City Health Safety Research Center), medical institutions were asked to report patients who had been diagnosed with influenza-like infections and exhibited severe abnormal behavior(Note) regardless of whether an influenza antiviral drug was used or not.

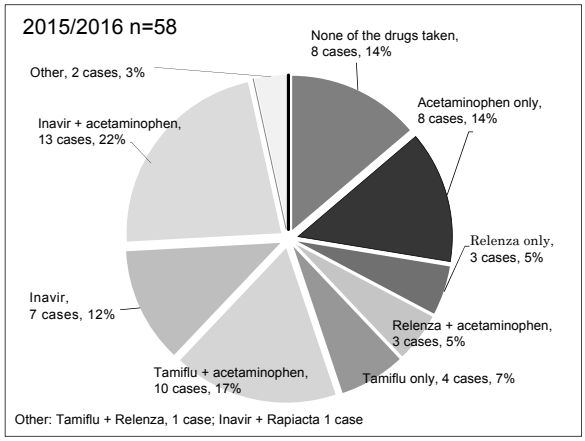
(Note) Behavior such as jumping down or sudden running, which could be life threatening if not stopped

<Conclusions of research team (summary)>

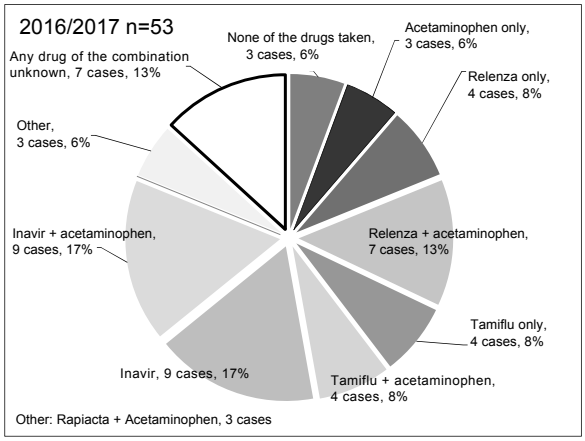
- The association between abnormal behavior and the type of influenza antiviral drug or whether such a drug was used or not is not considered to be limited to a specific pattern.
- In order to prevent serious outcomes due to abnormal behavior, precaution for such abnormal behavior after the onset of influenza symptom, is considered necessary regardless of whether influenza antiviral drugs have been prescribed or not.

Combination of drugs taken

○ 2015/2016 season



○ 2016/2017 season



[1] For the number of reported cases since the 2014/2015 season, refer to Document 3-1 from the 2017 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (8th meeting) held on November 9, 2017.
http://www.mhlw.go.jp/file/05-Shingikai-11121000-Iyakushokuhinkyoku-Soumuka/0000184039.pdf
(Only available in Japanese language)

History of safety measures for influenza antiviral drugs

○ On the basis of an event reported by media in February 2007 that a junior high school student who had taken Tamiflu fell to his death from his apartment building, healthcare providers have been alerted to take the preventive safety measure of explaining the following to patients and their families when the patient is being cared for at home, regardless of whether Tamiflu has been prescribed or not:
(1) Explain that there is a risk of abnormal behavior,
(2) They should take care not to leave the patient alone for at least 2 days.

○ Since it was later reported that a teenage patient fell from the 2nd floor and broke a bone after taking Tamiflu, a precautionary statement to the effect that healthcare professionals should as a general rule refrain from using Tamiflu in teenage patients, except in high-risk cases, was added (Refer to box below).
In addition, pharmaceutical companies were instructed to distribute "Dear Healthcare Professional Letters" to medical institutions, etc., and to caution them.

Warning (excerpt)
Abnormal behavior that has resulted in accidents such as falls has been reported in patients aged 10 to 19 years following administration of this drug, although the causal relationship to this drug is unknown. Generally, this drug should not be used in these patients for the above reason except that the patient may have a high risk based on complications and medical history, etc.
When this drug is administered to children and adolescents, it is required to explain to patients or their families that, after initiation of treatment with this drug, (1) abnormal behavior may occur and (2) caregivers should be careful not to leave patients alone at least for 2 days if they are treated at home, as preventative measures to avoid rare accidents.
Also, it has been reported that similar symptoms occur due to influenza encephalopathy, and it is required to explain the same as above.

○ Moreover, on the basis of the investigation by the Subcommittee on Drug Safety of the Committee on Drug Safety in the MHLW Pharmaceutical Affairs and Food Sanitation Council (hereinafter referred to as "Subcommittee on Drug Safety") on December 2007, necessity for an explanation to the effect that patients being cared for at home should not be left alone for at least 2 days was added to the "Important Precautions" section of the package inserts for Relenza, etc. (However, there was no statement that use should be avoided in teenage patients in principle).
The description in package inserts for Rapiacta and Inavir, which were approved for marketing in January 2010 and September 2010, respectively, has been aligned with that for Relenza.

○ The causal relationship between administration of Tamiflu and abnormal behavior, etc., was investigated by the Subcommittee on Drug Safety on the basis of epidemiological surveys, etc., and a report[2] was compiled in June 2009.

○ The report stated that since it was difficult to draw any clear conclusions about the causal relationship between Tamiflu and abnormal behavior, it would be appropriate to continue the same preventive measures that had been followed up, including refraining from using Tamiflu in patients in their teens.

○ Since the results of the 2009 investigation were compiled as well, the status of reporting of adverse drug reactions (ADRs) related to abnormal behavior for each season, etc., has been reported to the Subcommittee on Drug Safety Measure Research.

[2] Oseltamivir phosphate (Tamiflu) (Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council on June 16, 2009)
http://www.mhlw.go.jp/shingi/2009/06/s0616-5.html
(Only available in Japanese language)

2

Suspected Adverse Reactions to Influenza vaccines in the 2016 Season

1. Introduction

This section presents suspected adverse reaction to influenza vaccine reported from October 1, 2016 through April 30, 2017 (hereinafter referred to as the "2016 season").

If symptoms are diagnosed as an adverse reaction falling under the Reporting Criteria for suspected adverse reactions to influenza vaccines at medical institutions, this will be reported from medical institutions to MHLW regardless of causality. Data on reports by medical institutions are collected and evaluated by PMDA together with those reports by 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 suspected adverse reactions reports are investigated and reviewed on a regular basis at the joint meeting 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") to discuss the necessity of safety measures.[1]

2. Reports of suspected adverse reactions to influenza vaccines (2016 season)

(1) Number of reported suspected adverse reactions and reporting frequency

Table 1 shows the number of reported suspected adverse reactions 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 suspected adverse reactions and estimated number of vaccinated persons

	Reports by medical institutions*			Reports by MAHs (serious reports)**	
Estimated number of vaccinated persons (number of vaccinations)	Total number of reports (reporting frequency)	Number of reported serious cases (reporting frequency)	Number of reported death	Number of reported serious cases (reporting frequency)	Number of reported death
52 845 556 (As of April 30, 2017)	243 (0.0005%)	86 (0.0002%)	6 (0.00001%)	77 (0.00015%)	4 (0.000008%)

* The reports by medical institutions were of cases reported in accordance with Article 12-1 of the Preventative Vaccination Law (PV Law) or with Article 68-10-2 of the PMD Act.

** The reports by MAHs were of cases determined to be "serious" in accordance with Article 68-10-1 of the PMD Act. The reports by MAHs may duplicate some cases reported by medical institutions, and duplicate reports were added up as reported by medical institutions.

(2) Reported suspected adverse reactions by sex and age group

The number of reported suspected adverse reactions to influenza vaccines by sex and age group are shown 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	113	39
Female	130	34
Unknown	0	4
Total	243	77

Table 3 Number of reports by age group

Age group	Reports by medical institutions			Reports by MAHs	
	Total number of reports	Number of reported serious cases		Number of reported serious cases	
			Number of reported death		Number of reported death
0–9 years	79	28	0	23	0
10–19 years	22	8	0	2	0
20–29 years	20	6	0	4	0
30–39 years	20	10	1	7	0
40–49 years	27	7	0	10	0
50–59 years	18	4	2	6	0
60–69 years	15	3	1	6	1
70–79 years	15	3	0	7	0
80 years and older	27	17	2	9	2
Unknown	0	0	0	3	1
Total	243	86	6	77	4

(3) Details of reported symptoms

Suspected adverse reactions to influenza vaccines reported for the 2016 season are outlined by System Organ Class (SOC) in the right column of Table 4. There were no major changes compared with the 2015 season.

There were 10 cases of post-vaccination deaths reported, of which a direct causal relationship between the vaccination and the fatalities was not established for 9 cases as assessed by experts. According to the expert conclusion, in 1 case diagnosed as death due to acute disseminated encephalomyelitis (ADEM), a causal relationship between vaccination and the death could not be ruled out. ADEM is listed on the package insert of influenza vaccines as a clinically significant adverse reaction, and must be reported within 28 days after occurrence under the Reporting Criteria for suspected adverse reactions.

A total of 17 cases (Note 1) were reported as possible Guillain-Barre syndrome or ADEM. Of these, 6 cases and 2 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, 8 cases were assessed as Level 3 or higher anaphylaxis using the Brighton Criteria (8 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 August 2017, it was determined that there were no new concerns regarding safety of vaccines, including other reported symptoms, and it was decided that taking actions such as revision of package inserts would not be necessary at present but continuous caution will be exercised for the status of reports and their details.

Note1) Cases reported with the symptom name “Guillain-Barre syndrome” or “ADEM,” and those which are suspected to be Guillain-Barre syndrome or ADEM based on their clinical course.

Note2) Cases reported with the symptom name “anaphylaxis,” “anaphylactic reaction,” “anaphylactic shock,” “anaphylactoid reaction,” or “anaphylactoid shock.”

Table 4 Comparison of the number of suspected adverse reaction reports between the 2015 and 2016 seasons (by SOC)

	2015 season		2016 season	
	Tetravalent influenza vaccine (seasonal trivalent and H1N1)		Tetravalent influenza vaccine (seasonal trivalent and H1N1)	
SOC of symptom	Reports by medical institutions (serious reports)	Reports by MAHs	Reports by medical institutions (serious reports)	Reports by MAHs
Blood and lymphatic system disorders	3	1	6	6
Cardiac disorders	1	2	2	1
Congenital, familial and genetic disorders	1	0	0	0
Ear and labyrinth disorders	0	1	0	0
Endocrine disorders	1	0	0	1
Eye disorders	4	1	5	1
Gastrointestinal disorders	7	9	10	5
General disorders and administration site conditions	55	60	42	34
Hepatobiliary disorders	3	3	3	3
Immune system disorders	16	9	12	5
Infections and infestations	12	7	12	13
Investigations	2	2	4	5
Metabolic and nutritional disorders	1	7	2	0
Musculoskeletal and connective tissue disorders	4	10	5	4
Nervous system disorders	31	24	31	25
Psychiatric disorders	1	0	1	0
Renal and urinary disorders	3	1	5	5
Respiratory, thoracic and mediastinal disorders	11	11	7	4
Skin and subcutaneous tissue disorders	16	14	7	14
Vascular disorders	6	4	2	0
Total	178	166	156	126

3. Future safety measures

As detailed in “Reporting Suspected Adverse Reactions for Routine Vaccination,”[2] medical institutions are encouraged to promptly report any symptoms considered to meet the Suspected Adverse Reaction Reporting Criteria even if the causality is unclear.

In addition, medical institutions are requested to continue to exercise caution in the 2017 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 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 to gather safety information on the influenza vaccine including suspected adverse reaction reports and to adopt safety measures.

< References >

1) MHLW: Distributed Material 8 for the Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council (the 29th meeting) and the 2017 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (the 5th meeting) (the Joint Meeting), Reports of Adverse Reaction to Influenza Vaccines
http://www.mhlw.go.jp/file/05-Shingikai-10601000-Daijinkanboukouseikagakuka-Kouseikagakuka/0000175591.pdf
(Only available in Japanese language)

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 July 16, 2014, September 26, 2014, November 25, 2014, August 30, 2016, and September 25, 2017)
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/dl/170925-01c.pdf
(Only available in Japanese language)

Report form
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/hukuhannou_houkoku/dl/youshiki_01.pdf
(Only available in Japanese language)
Report entry application (National Institute of Infectious Diseases)
http://www.nih.go.jp/niid/ja/vaccine-j/6366-vaers-app.html
(Only available in Japanese language)

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 specific time frame is subject to mandatory reporting to MHLW regardless of causality according to the PV Law and associated 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) 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 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 (1) to (8)

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Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notifications dated November 28, 2017, the contents of important revisions and a case summary that served as the basis for these revisions are provided in this section.

1 Clozapine

Brand name (name of company)	Clozaril Tablets 25 mg and 100 mg (Novartis Pharma K.K.)
Therapeutic category	Psychotropics
Indications	Treatment-resistant schizophrenia

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Non-infectious pleurisy may occur. Patients should promptly undergo chest X ray or other necessary tests if dyspnoea, pyrexia, chest pain, etc. are observed. If any abnormalities are observed, make a differential diagnosis for infections and take appropriate measures such as discontinuation of the drug.

Reference information

The number of reported adverse reactions (for which a causality to the drug could not be ruled out) in approximately the last 3 years and 4 months (April 2014 to August 2017)
Cases related to scleritis: 1 case (no fatal case)
The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 3 000
Launched in Japan: July 2009

Case Summary

No.	Patient		Daily dose	Adverse reactions
	Gender/ Age	Reason for use (complications)	Treatment duration	Clinical course and Therapeutic measures
1	Male 50s	Schizophrenia (none)	12.5mg for 1 day ↓ Unknown dose for 10 days ↓ 125mg for 2 days ↓ 50mg for 2 days ↓ 25mg for 1 day	**Pleuritis** Day 1 of administration: Administration of clozapine(12.5 mg/day) started Day 14 of administration: Pyrexia and chest pain; serositis (pleuritis) suspected. Also abnormal laboratory test results. Dosage reduced to 50 mg/day. Day 15 of administration: CT: pleural effusion (+), CRP increased (2.3 mg/dL), AST/ALT normal ECG: normal, troponin T negative Day 16 of administration: Dosage reduced to 25 mg (Administered in morning only; evening dose temporarily discontinued). Day 17 of administration: Administration of drug discontinued. 2 days after discontinuation: CT: pleural effusion (++), pericardial effusion (+), troponin T (+) 3 days after discontinuation: Fever alleviated, CT: pleural effusion (+), pericardial effusion (+), troponin T (+), CRP (11.0), no subjective symptoms 4 days after discontinuation: No subjective symptoms, troponin T (-)

Laboratory Examination

	Day 14 of administration	Day 15 of administration	Day 17 of administration	3 days after discontinuation	4 days after discontinuation	6 days after discontinuation	12 days after discontinuation	19 days after discontinuation	26 days after discontinuation	81 days after discontinuation
Body temperature (°C)	38.1		38.8	37.3	37.2	36.6	36.4	36.4	36.8	36.4
CRP (mg/dL)		2.3	15.4	11.0	7.1	2.4				
White blood cell count (/μL)	13 400		11 800	10 600	11 300	11 200	12,400	8 000	6 900	5 700
Neutrophils (%)	97.1		88.6	80.6	81.2	77.1				
Eosinophils (%)	1.0		1.1	1.3	2.0	2.9	26.8	21.1	19.6	1.0
AST (IU/L)		16	145	73	36	55				
ALT (I IU/L)		32	255	274	185	178				
LDH (IU/L)			345	238	207	207				
Cardiac troponin T		-	+	+	-	-				
CK-MB (I IU/L)	16		8	8	7	6				

Concomitant medications: none

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Revision of Precautions (No. 290)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs in accordance with the Notifications dated November 28, 2017

1 Psychotropics

Clozapine

Brand name	Clozaril Tablets 25 mg and 100 mg (Novartis Pharma K.K.)
Adverse reactions (clinically significant adverse reactions)	Pleurisy: Non-infectious pleurisy may occur. Patients should promptly undergo chest X ray or other necessary tests if dyspnoea, pyrexia, chest pain, etc. are observed. If any abnormalities are observed, make a differential diagnosis for infections and take appropriate measures such as discontinuation of the drug.

2 Diagnostic agents-Miscellaneous

a. Gadoxetate sodium
b. Gadoteridol
c. Meglumine gadoterate
d. Gadobutrol

Brand name	a. EOB·Primovist Injection Syringe 5 mL and 10 mL (Bayer Yakuhin, Ltd.) b. ProHance for Intravenous Injection 5 mL, 10 mL, 15 mL and 20 mL, ProHance for Intravenous Injection Syringe 13 mL and 17 mL (Bracco-Eisai Co., Ltd.) c. Magnescope Intravenous Injection 38% Syringe 10 mL, 11 mL, 13 mL, 15 mL and 20 mL (Guerbet Japan K.K.) d. Gadovist IV Injection 1.0 mol /L Syringe 5 mL, 7.5 mL and 10 mL (Bayer Yakuhin, Ltd.)
Precautions Concerning Indications	It has been reported that high signal intensity was observed in the cerebellar dentate nucleus and globus pallidus on unenhanced T1-weighted MR images and that gadolinium was detected in autopsied brain tissues in patients who received a gadolinium-based contrast agent several times. The necessity of MRI scan using gadolinium -based contrast agents should be determined carefully.

3 **Diagnostic agents-Miscellaneous**

a. Gadodiamide hydrate
b. Meglumine gadopentetate

Brand name	a. Omniscan Intravenous Injection 32%, Omniscan Intravenous Injection 32% Syringe 5 mL, 10 mL, 15 mL and 20 mL (Daiichi Sankyo Co. Ltd. and the others) b. Magnevist IV Injection 10 mL, 15 mL, 20 mL and 30 mL, Magnevist IV Injection Syringe 5 mL, 10 mL, 15 mL and 20 mL (Bayer Yakuhin, Ltd. and the others)
Precautions Concerning Indications	It has been reported that high signal intensity was observed in the cerebellar dentate nucleus and globus pallidus on unenhanced T1-weighted MR images and that gadolinium was detected in autopsied brain tissues in patients who received a gadolinium-based contrast agent several times. The necessity of MRI scan using gadolinium-based contrast agents should be determined carefully. It has been reported that more gadolinium remained in the brain with linear gadolinium-based contrast agents containing this drug than with macrocyclic gadolinium-based contrast agents. This drug should be administered when macrocyclic gadolinium-based contrast agents are not appropriate.

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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 Marketing Authorization Holder (MAH) is responsible for collecting 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 31, 2017)
◎: Products for which EPPV was initiated after November 1, 2017

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
◎	Glecaprevir hydrate/pibrentasvir Maviret Combination Tablets	AbbVie GK	November 27, 2017
◎	Rupatadine fumarate Rupafin Tablets 10 mg	Teikoku Seiyaku Co., Ltd.	November 27, 2017
◎	Avelumab (genetical recombination) Bavencio Intravenous Injection 200 mg	Merck Serono Co., Ltd.	November 22, 2017
◎	Daratumumab (genetical recombination) Darzalex Intravenous Infusion 100 mg, 400 mg	Janssen Pharmaceutical K.K.	November 22, 2017
◎	Flutemetamol (^{18}F) Vizamyl Intravenous Injectable	Nihon Medi-Physics Co., Ltd.	November 10, 2017
	Quetiapine fumarate[*1] Bipresso Extended Release Tablets 50 mg, 150 mg	Astellas Pharma Inc.	October 27, 2017
	Sildenafil citrate Revatio Tablets 20 mg	Pfizer Japan Inc.	September 27, 2017
	Nusinersen sodium[*2] Spinraza Intrathecal Injection 12 mg	Biogen Japan Ltd.	September 22, 2017
	Lyophilized human prothrombin complex concentrate Kcentra for I.V. Injection 500, 1000	CSL Behring K.K.	September 19, 2017
	Teneligliptin hydrobromide hydrate/ Canagliflozin hydrate Canalia Combination Tablets	Mitsubishi Tanabe Pharma Corporation	September 7, 2017
	Amenamevir Amenalief Tab. 200 mg	Maruho Co., Ltd.	September 7, 2017
	Baricitinib Olumiant Tablets 2 mg, 4 mg	Eli Lilly Japan K.K.	September 1, 2017
	Pralatrexate Difolta Injection 20 mg	Mundipharma K.K.	August 30, 2017
	Nusinersen sodium Spinraza Intrathecal injection 12 mg	Biogen Japan Ltd.	August 30, 2017

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
	Leuprorelin acetate[*3] Leuplin SR for Injection Kit 11.25 mg	Takeda Pharmaceutical Company Limited	August 25, 2017
	Eltrombopag olamine[*4] Revolade Tablets 12.5 mg, 25 mg	Novartis Pharma K.K.	August 25, 2017
	Lyophilized human antithrombin III concentrate[*5] Kenketu Nonthron 500 for Injection, 1500 for Injection	Nihon Pharmaceutical Co., Ltd.	August 25, 2017
	Florbetapir (^{18}F) Amyvid Injection	Fujifilm RI Pharma Co., Ltd.	August 21, 2017
	Clobetasol propionate Comclo Shampoo 0.05%	Maruho Co., Ltd.	July 11, 2017
	Denosumab (genetical recombination) [*6] Pralia Subcutaneous Injection 60 mg Syringe	Daiichi Sankyo Company, Limited	July 3, 2017
	Fluvoxamine maleate (1) Luvox Tablets 25 mg, 50 mg, 75 mg (2) Depromel Tablets 25 mg, 50 mg, 75 mg	(1) AbbVie GK (2) Meiji Seika Pharma Co., Ltd.	July 3, 2017
	Hydromorphone hydrochloride Narurapid Tablets 1 mg, 2 mg, 4 mg, Narusus Tablets 2 mg, 6 mg, 12 mg, 24 mg	Daiichi Sankyo Propharma Co., Ltd.	June 19, 2017
	Naldemedine tosilate Symproic Tablets 0.2 mg	Shionogi & Co., Ltd.	June 7, 2017

*1 Depressive symptoms in bipolar disorder
*2 Spinal muscular atrophy
*3 Suppression of progression of congenital bulbospinal muscular atrophy
*4 Aplastic anaemia
*5 Portal vein thrombosis associated with decreased antithrombin III
*6 Suppression of progression of bone erosion associated with rheumatoid arthritis