Pharmaceuticals and Medical Devices Safety Information

No. 339 December 2016

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Pharmaceuticals and Medical Devices Safety Information

No. 339 December 2016

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

[Outline of Information]

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
Alb	Albumin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BP	Bullous pemphigoid
BUN	Blood urea nitrogen
CPR	C-peptide immunoreactivity
Cr	Creatinine
CRP	C-reactive protein
Cu	Copper
DIHS	Drug-induced hypersensitivity syndrome
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal year
GA	Glycated albumin
Hb	Hemoglobin
HHV-6	Human herpes virus-6
HLA	Human leukocyte antigen
HSB	Health Service Bureau
HSIB	Health Services and Infections Bureau
Ht	Hematocrit
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IIF	Indirect immunofluorescent
IRI	Immunoreactive insulin
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
PFSB	Pharmaceutical and Food Safety Bureau
Plt	Platelet
PMDA	Pharmaceuticals and Medical Devices Agency
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
RBC	Red blood cells
SD	Safety Division
SNRI	Serotonin-noradrenaline reuptake inhibitor
SOC	System organ class
SSRI	Selective serotonin reuptake inhibitor
VCA	Viral capsid antigen
WBC	White blood cells
Zn	Zinc

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Precautions for Driving, etc. under the Treatment with Milnacipran Hydrochloride, Duloxetine Hydrochloride, or Venlafaxine Hydrochloride

Active ingredient	(1) Milnacipran hydrochloride (2) Duloxetine hydrochloride (3) Venlafaxine hydrochloride
Brand name (name of company)	(1) Toledomin Tablets 12.5 mg, 15 mg, 25 mg, 50 mg (Asahi Kasei Pharma Corporation) and the others (2) Cymbalta Capsules 20 mg, 30 mg (Shionogi & Co., Ltd.) (3) Effexor SR Capsules 37.5 mg, 75 mg (Pfizer Japan Inc.)
Therapeutic category	Serotonin-noradrenaline reuptake inhibitors (SNRIs)
Indications	(1) Depression/depressed state (2) Depression/depressed state Pain accompanying the following diseases Diabetic neuropathy, fibromyalgia, chronic lumbago (3) Depression/depressed state

1. Introduction

Milnacipran hydrochloride, duloxetine hydrochloride, and venlafaxine hydrochloride are serotonin-noradrenaline reuptake inhibitors (SNRIs). Milnacipran hydrochloride was approved in September 1999 for the indication “depression/depressed state,” followed by approvals for the same indication in January 2010 for duloxetine hydrochloride and in September 2015 for venlafaxine hydrochloride. Duloxetine hydrochloride has additionally been approved for “pain accompanying diabetic neuropathy (approved in February 2012),” “pain accompanying fibromyalgia (approved in May 2015),” and “pain accompanying chronic lumbago (approved in March 2016).”

Since the times of their approval, the “Important Precautions” section for each of these 3 SNRIs (the SNRI, applicable to any one, two, or all three products) has contained the following precaution prohibiting driving a car or operating other hazardous machinery (driving etc.): “as symptoms such as somnolence and dizziness may occur, caution patients not to engage in hazardous machine operation, such as driving a car, during the treatment.” However, the “Important Precautions” sections for selective serotonin reuptake inhibitors (SSRIs), which are similar drugs, state that “as symptoms such as somnolence and dizziness may occur, caution patients about operating hazardous machines such as driving a car,” and thus driving etc., is not prohibited, with the exception of some drugs (see Table 1).

Recently, on November 25, 2016, Ministry of Health, Labour and Welfare (MHLW) has instructed revisions to the “Precautions” based on the investigation at the 6th Meeting of the Subcommittee on Drug Safety of the Committee on Drug Safety in Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council (“Subcommittee on Drug Safety”) in fiscal year (FY) 2016, held on October 25, 2016. This section presents the precautions to be taken when a patient wants to drive etc. during treatment with the SNRI.

Table 1 Precautions in the package inserts of serotonin-noradrenaline reuptake inhibitors (SNRIs)

Active ingredient Brand name (name of marketing authorization holder [MAH])	Before revision
Milnacipran hydrochloride Toledomin Tablets 12.5 mg, 15 mg, 25 mg, 50 mg, etc. (Asahi Kasei Pharma Corporation) and the others	2. Important Precautions 5) As symptoms such as somnolence and dizziness may occur, caution patients not to engage in hazardous machine operation such as driving a car during the treatment.
Duloxetine hydrochloride Cymbalta Capsules 20 mg, 30 mg (Shionogi & Co., Ltd.)	2. Important Precautions (7) As symptoms such as somnolence and dizziness may occur, caution patients not to engage in hazardous machine operation such as driving a car during the treatment.
Venlafaxine hydrochloride Effexor SR Capsules 37.5 mg, 75 mg (Pfizer Japan Inc.)	2. Important Precautions (6) As symptoms such as somnolence and dizziness may occur, caution patients not to engage in hazardous machine operation such as driving a car during the treatment.

(Reference) Selective serotonin reuptake inhibitors (SSRIs)

Active ingredient Brand name (name of MAH)	Current version
Escitalopram oxalate Lexapro Tablets 10 mg (Mochida Pharmaceutical Co., Ltd.)	2. Important Precautions (5) As symptoms such as somnolence and dizziness may occur, caution patients about operating hazardous machine such as driving a car during the treatment.
Sertraline hydrochloride Jzoloft Tablets 25 mg, 50 mg, 100 mg, etc. (Pfizer Japan Inc.) and the others	2. Important Precautions (5) As symptoms such as somnolence and dizziness may occur, caution patients about operating hazardous machine such as driving a car.
Paroxetine hydrochloride hydrate Paxil Tablets 5 mg, 10mg, 20 mg, etc. (GlaxoSmithKline K.K.) and the others	2. Important Precautions (1) As symptoms such as somnolence and dizziness may occur, caution patients about operating hazardous machine such as driving a car. These symptoms are frequently observed at an early stage of administration.
Fluvoxamine maleate Luvox/Depromel Tablets 25 mg, 50 mg, 75 mg, etc. (AbbVie GK/Meiji Seika Pharma Co., Ltd.) and the others	2. Important Precautions 1) As consciousness disturbance such as depressed level of consciousness and loss of consciousness may occur, caution patients not to engage in hazardous machine operation such as driving a car during the treatment.

2. Investigation results relating to the effect of SNRIs on driving, etc., and revision of package inserts

The results of the investigation conducted this time on 21 events[1)] that may affect driving, etc. (“driving-related events”) from the adverse drug reactions (ADRs) reported in Japan, occurrences of road traffic accidents overseas, and the results of clinical studies that assessed the effect of the SNRI on driving performance, were as follows.

[1)] Depressed level of consciousness, loss of consciousness, altered state of consciousness, mental impairment, stupor, syncope, sudden onset of sleep, somnolence, hypersomnia, lethargy, vertigo, dizziness postural, dizziness, disturbance in attention, amnesia, amnestic disorder, transient global amnesia, retrograde amnesia, memory impairment, accident, and road traffic accident

- In clinical studies assessing the effect of the SNRI on driving, it was not suggested that the SNRI reduced driving performance relative to administration of placebo or when not administered
- In Japanese and overseas clinical studies, comparison of safety profiles of these drugs with SSRIs did not show a greater number of occurrences of adverse reactions that may affect driving, etc.
- Pharmacologically, no major differences from SSRIs were found in their affinity to receptors relating to dizziness, sedation, or sleepiness
- In Japan, the common driving-related events reported, including somnolence, dizziness, and postural dizziness, were frequently observed at early stages of administration
- There have been reports of consciousness disturbance-related events that may affect driving while patients themselves are unaware of signs of the event,[2] but the possible influence of concomitant medication or the patient's condition could not be ruled out for any of these events, and there were no cases showing an obvious relationship with the SNRI
- There were no cases of road traffic accidents in Japan with an obvious relationship between a consciousness disturbance-related event and the SNRI
- In overseas countries where driving, etc. is not prohibited, there are not many accumulated reports of accidents during treatment with the SNRI

Based on these investigation results, the Subcommittee on Drug Safety determined that the precautions can be revised for driving, etc. under the treatment with the SNRI in line with the precautions for SSRIs to allow flexible handling depending on the patient's situation, rather than uniform prohibition. However, as there have been more than a few reports of adverse reactions that may affect driving, etc. such as somnolence and dizziness, it was considered to be necessary to instruct patients not to drive under any circumstances when experiencing these adverse reactions.

The investigation results showed that for all the SNRI, adverse reactions such as somnolence and dizziness tend to occur at an early stage after the start of administration. However, this may also be when switching from another drug as well as when administration is started, and the possibility of an influence from the condition of the patient when administration is started cannot be ruled out. Therefore, it was decided that pharmaceutical companies should prepare materials to provide the information.

For the revision of precautions as of November 25, 2016, see "5. Revision of Precautions (p. 28)".

3. Precautions for physicians and patients who want to drive etc.

The Subcommittee for Drug Safety discussed what precautions should be taken by physicians and by patients when patients want to drive, etc. during treatment with the SNRI. For example, it was pointed out that, depending on the patient's background (including conditions of psychiatric illness, complications, or concomitant medications), there may be cases where the patient receiving the SNRI should not drive, etc. and that it is necessary for the prescribing physician to monitor the patient carefully, determine whether or not it is appropriate for the patient to drive, etc., and give instructions to the patient. Based on the deliberation in the Subcommittee for Drug Safety, the precautions for physicians and patients who want to drive, etc. were summarized as shown in Table 2.

In order to provide information about these precautions to clinical practices, MHLW instructed the MAHs for the SNRI to prepare informational materials containing these precautions for healthcare providers and for patients.

If a patient being prescribed the SNRI wants to drive, etc., healthcare providers should make a decision on whether driving, etc., is appropriate, bearing these precautions in mind, and give patients necessary instructions.

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[2] Depressed level of consciousness, loss of consciousness, altered state of consciousness, stupor, and syncope

Table 2 Precautions for physicians and patients who want to drive, etc.

1. Precautions to be taken by a physician when a patient being prescribed the SNRI wants to drive, etc.
   (1) Monitor the patient carefully to determine whether the condition of the patient's depression or other psychiatric illness is stable.
   (2) Adhere to the dosage and administration.
   (3) Considering the individual variations in the effects of the SNRI on patients, monitor individual patients carefully.
   (4) As adverse reactions such as dizziness and somnolence that may affect driving, etc., may occur with the administration of the SNRI, check the patient for any subjective symptoms.
   (5) At the early stages of administration, when switching from another drug, and when changing dosages, it is necessary to pay particular attention to whether the dose is proper for the patient and whether the condition of the patient's psychiatric illness is stable. For this reason, consider monitoring the patient for a certain period before determining whether or not to allow the patient to drive, etc.
   (6) Avoid prescribing multi-drug therapy and try to make simple and minimal prescription plans. Since concomitant medications make it difficult to predict the effect on driving, etc., it may be appropriate to caution the patient to avoid driving, etc.
2. Precautions to be taken by a patient when prescribed the SNRI and driving a car, etc.
   (1) Adverse reactions such as dizziness or somnolence that may affect driving, etc., may occur with the administration of the SNRI.
   (2) At times such as at the early stages of administration, when switching from another drug, and when changing dosages, driving, etc. should be avoided as far as possible, as the above adverse reactions are more likely to occur, and if poor physical condition, for example somnolence or lack of sleep, is noticed, driving, etc. should absolutely be avoided.

4. Conclusion

The current revision of the "Precautions" does not unconditionally allow driving, etc. while receiving the SNRI, which was uniformly prohibited previously. The physician prescribing the SNRI must carefully monitor the condition of the patient's psychiatric illness and the occurrences of adverse reactions to determine whether or not to allow the patient to drive, etc. The patient on the other hand must be instructed to pay attention to the occurrence of adverse reactions and physical deconditioning and must not drive, etc., under any circumstances if experiencing these. Healthcare professionals are requested to understand the intention of the current revision and further cooperate in the proper use of the SNRI.

<References>

Material 2 for the 2016 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (6th meeting held on October 25, 2016)
https://www.pmda.go.jp/files/000215084.pdf

Revision of Precautions (Pharmaceutical Safety and Environmental Health Bureau [PSEHB]/Safety Division [SD] Notification No. 1125-1, dated November 25, 2016)
https://www.pmda.go.jp/files/000215083.pdf

Informing related parties or the Revision of Precautions for duloxetine hydrochloride, venlafaxine hydrochloride, milnacipran hydrochloride (for Request) (PSEHB/SD Notification No. 1125-2 and 1125-3, dated November 25, 2016)
http://www.mhlw.go.jp/file/06-Seisakujouhou-11120000-Iyakushokuhinkyoku/0000143869.pdf
(Only available in Japanese language)

2

Suspected Adverse Reactions to Influenza Vaccines in the 2015 Season

1. Introduction

This section presents suspected adverse reactions to influenza vaccines reported from October 1, 2015 through April 30, 2016 (hereinafter referred to as "the 2015 season").

If symptoms are diagnosed as an adverse reaction falling under the Reporting Criteria for suspected adverse reactions to influenza vaccines at a medical institution, this will be reported from the medical institution to MHLW regardless of causality. Data on reports by medical institutions are collected and evaluated by Pharmaceuticals and Medical Devices Agency (PMDA) together with those reported 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 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 suspected adverse reactions to influenza vaccines (2015 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 serious cases (reporting frequency)	
			Number of reported deaths		Number of reported deaths
51 442 374 (as of April 30, 2016)	288 (0.0006%)	100 (0.0002%)	4 (0.00001%)	95 (0.0002%)	3 (0.000006%)

*The reports by MAHs were of cases determined to be "serious" in accordance with Article 68-10 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices, and may duplicate with some cases reported by medical institutions. Duplicate reports were added up as reports by medical institutions.

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

The numbers of reported suspected adverse reactions to influenza vaccines by sex and age group are shown in Table 2 and 3, respectively.

Table 2 Number of reports by sex

Sex	Number of reports by medical institutions	Number of reports by MAHs
Male	134	46
Female	154	46
Unknown	0	3
Total	288	95

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 deaths		Number of reported deaths
0-9 years	87	33	1	30	0
10-19 years	22	9	0	7	0
20-29 years	22	2	0	6	0
30-39 years	31	10	0	5	0
40-49 years	29	7	0	5	0
50-59 years	15	5	0	6	0
60-69 years	22	6	1	10	0
70-79 years	39	16	0	6	0
80 years and older	21	12	2	15	3
Unknown	0	0	0	5	0
Total	288	100	4	95	3

(3) Details of reported symptoms

Suspected adverse reactions to influenza vaccines reported for the 2015 season are outlined by System Organ Class (SOC) in the right column of Table 4. In comparison with the 2014 season, reports increased on symptoms classified as general disorders and administration site conditions (such as injection site erythema, injection site pain, and pyrexia).

There were 7 cases of post-vaccination deaths reported, of which a direct causal relationship between the vaccination and the fatalities was not established for 6 cases as assessed by experts. According to expert opinions, 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, 7 cases and 6 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 35 cases[Note 2] were reported as possible anaphylaxis. Of these, 8 cases were assessed as Level 3 or higher anaphylaxis using the Brighton Criteria (5 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 July 2016, 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 paid to the status of reports and their details.

Note 1: 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.
Note 2: Cases reported with the symptom name “anaphylactic reaction,” “anaphylactic shock,” “anaphylactoid reaction,” or “anaphylactoid shock.”

Table 4 Comparison of the number of suspected adverse reaction reports between the 2014 and 2015 seasons (by SOC)

	2014 season		2015 season	
	Trivalent influenza vaccine (seasonal bivalent and H1N1)		Quadrivalent 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 disorder	3	3	3	1
Cardiac disorders	2	0	1	2
Congenital, familial and genetic disorders	0	0	1	0
Ear and labyrinth disorders	0	0	0	1
Endocrine disorders	0	0	1	0
Eye disorders	0	2	4	1
Gastrointestinal disorders	3	5	7	9
General disorders and administration site conditions	28	27	55	60
Hepatobiliary disorders	4	1	3	3
Immune system disorders	15	6	16	9
Infections and infestations	15	8	12	7
Investigations	2	8	2	2
Metabolism and nutrition disorders	0	2	1	7
Musculoskeletal and connective tissue disorders	7	6	4	10
Nervous system disorders	30	12	31	24
Renal and urinary disorders	5	3	3	1
Respiratory, thoracic and mediastinal disorders	13	5	11	11
Skin and subcutaneous tissue disorders	13	14	16	14
Vascular disorders	3	1	6	4
Injury, poisoning and procedural complications	1	0	0	0
Psychiatric disorders	0	0	1	0
Social circumstances	1	0	0	0
Total	145	103	178	166

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 2016 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 suspected adverse reaction reports and to adopt safety measures.

<References>

1 MHLW: Distributed Material 8 for the Adverse Reaction Review Committee for Preventative/Voluntary Vaccination in the Health Sciences Council (the 20th meeting) and the 2016 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (the 4th meeting) (the Joint Meeting), Report of Adverse Reaction to Influenza Vaccines
http://www.mhlw.go.jp/file/05-Shingikai-10601000-Daijinkanboukouseikagakuka-Kouseikagakuka/0000129916.pdf
(Only available in Japanese language)

2 Reporting Suspected Adverse Reactions for Routine Vaccination, etc.: Health Service Bureau (HSB) Notification No. 0330-3 and Pharmaceutical and Food Safety Bureau (PFSB) Notification No. 0330-1, by the Director-General of HSB and PFSB, dated March 30, 2013 (partially amended July 16, 2014, September 26, 2014, November 25, 2014, and August 30, 2016)
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/dl/160830-01c.pdf
(Only available in Japanese language)

Report form:
http://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/saishin.pdf
(Only available in Japanese language)
Description guidelines:
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/dl/yobou140926-5.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 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
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 Preventative Vaccination 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 or 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 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)

3

Safety of Influenza Antiviral Drugs

1. Introduction

The 2016 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council held a 7th meeting on November 4, 2016 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, MHLW has issued notifications regarding "Calling attention to the Precautions against Influenza Antiviral Drugs" [PSEHB/SD Notification No. 1118-3 to 1118-7 dated November 18, 2016] to MAHs so that they will encourage healthcare providers to exercise caution.

This section will provide an overview of the adverse reaction related to influenza antiviral drugs reported for the 2015/2016 season (September 1, 2015 to August 31, 2016) 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 in FY 2015 by the Japan Agency for Medical Research and Development (Research on Regulatory Science of Pharmaceuticals and Medical Devices) (Chief Researcher: Director Nobuhiko Okabe, Kawasaki City Health Safety Research Center) for the 2015/2016 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 influenza antiviral drug 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/0000142736.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 in the 2015/2016 season reported to PMDA based on the Pharmaceuticals and Medical Devices Act. The results are almost comparable to the previous season. A total of 7 fatal cases were reported; however, with the exception of one fatal case due to anaphylactoid shock associated with Rapiacta for which it was determined that a causal relationship could not be ruled out, 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

	2015/2016 season (Sept. 1, 2015 to Aug. 31, 2016)			2014/2015 season (Sept. 1, 2014 to Aug. 31, 2015)		
	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	25	1	Approximately 3 050 000	24	5	Approximately 2 880 000
Of which, those younger than 10 years old	17	0	Approximately 1 470 000	12	0	Approximately 1 140 000
Of which, those aged 10 to 19 years	0	0	Approximately 85 000	2	0	Approximately 70 000
Of which, those that are "pediatric" [Note 2]	1	0	-	2	0	-
Relenza	4	1	Approximately 2 550 000	3	0	Approximately 1 370 000
Of which, those younger than 10 years old	0	0	Approximately 1 010 000	0	0	Approximately 280 000
Of which, those aged 10 to 19 years	2	1	Approximately 810 000	3	0	Approximately 650 000
Rapiacta	0	3	Approximately 290 000	0	2	Approximately 210 000
Of which, those younger than 10 years old	0	0	Approximately 30 000	0	0	Approximately 20 000
Of which, those aged 10 to 19 years	0	0	Approximately 40 000	0	0	Approximately 30 000
Inavir	11	2	Approximately 3 920 000	5	1	Approximately 3 800 000
Of which, those younger than 10 years old	0	0	Approximately 470 000	0	0	Approximately 380 000
Of which, those aged 10 to 19 years	8	0	Approximately 1 050 000	3	0	Approximately 1 060 000

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 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, or of the type of influenza antiviral drug 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 on national trends relating to abnormal behavior during influenza-like infections 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 on National Trends Relating to Abnormal Behavior During Influenza-like Infections" (Health Services and Infections Bureau [HSIB]

Notification No. 1118-1 and PSEHB/SD Notification No. 1118-1 dated November 18, 2016 as well as HSIB Notification No. 1118-2 and PSEHB/SD Notification No. 1118-2 dated the same day).

[References]

• Materials from the 2016 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (7th meeting):
http://www.mhlw.go.jp/stf/shingi2/0000142734.html
(Only available in Japanese language)
• Comprehensive policy on influenza (winter FY 2016):
http://www.mhlw.go.jp/bunya/kenkou/influenza/index.html
(Only available in Japanese language)
• Influenza Q&A 2016:
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou01/qa.html
(Only available in Japanese language)

4

Important Safety Information

Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated November 22, 2016, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Polaprezinc

Brand name (name of company)	Promac Granules 15 %, Promac D Tablets 75 mg (Zeria Pharmaceutical Co., Ltd.), and the others
Therapeutic category	Peptic ulcer agents
Indications	Gastric ulcer

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Copper deficiency: Copper deficiency may occur because polaprezinc contains zinc, which inhibit the absorption of copper. Pancytopenia and anaemia associated with copper deficiency have been reported in poorly nourished patients. If any abnormalities are observed, appropriate measures should be adopted.

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 5 months (April 2013 to September 2016).
Cases related to copper deficiency: 8 cases* (no fatal case)
* 4 cases were for a condition not included in the approved indications

The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 1 100 000

Launched in Japan: October 1994 (Promac granules 15%)
July 2006 (Promac D tablets 75)

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
1	Female 40s	Gastric ulcer (chronic renal failure, hyperlipidaemia, antiphospholipid syndrome, multiple cerebral microinfarcts, secondary hyperparathyroidism, hyperphosphataemia, diarrhoea, insomnia, nephrogenic anaemia)	150 mg Approximately 10 years	Pancytopenia (copper deficiency) Before the start of administration The patient was receiving long-term hemodialysis for chronic renal failure. At onset (approximately Year 10 of administration) Inappetence and general malaise were observed, and pancytopenia also occurred. Approximately 1 month before onset, gastroenteritis occurred, and a period of Impaired eating ability had been observed. Tests were conducted subsequently, and

				excessive zinc (Zn, 182 μg/dL) and copper deficiency (Cu, ≤4 μg/dL) were observed. The cause was investigated, and it was found that the patient had been taking polaprezinc at 150 mg/day for approximately 10 years. The event was determined to be pancytopenia caused by acquired Cu deficiency due to excessive Zn, and administration of polaprezinc was discontinued. Approximately 1 month after discontinuation With discontinuation of polaprezinc alone, there was little resolving in Cu deficiency, and therefore drinking of 1 cup of cocoa per day was started to supplement Cu levels. Approximately 2 months after discontinuation Serum Zn and serum Cu levels were resolving, and increases in blood cell levels were observed. It was determined that the event had resolved. After drinking of cocoa was discontinued, no cytopenia was observed.
	Concomitant medications: aspirin, sodium rabeprazole, pravastatin sodium, cinacalcet hydrochloride, calcitriol, sevelamer hydrochloride, clostridium butyricum formulation, zolpidem tartrate, darbepoetin alfa (genetical recombination)			

Laboratory examination

	At onset	Approximately 1 month after discontinuation	Approximately 2 months after discontinuation
RBC (×10^4/μL)	−	271	315
Hb (g/dL)	7.8	9.2	10.2
Ht (%)	−	30	33.1
WBC (μL)	1410	2500	5430
Plt (×10^4/μL)	7.3	17.8	17
Zn (μg/dL)	182	107	81
Cu (μg/dL)	≤4	≤4	58

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
2	Male 70s	Gastric ulcer (myelodysplastic syndrome, dysphagia, Parkinson's syndrome, angina pectoris, chronic bronchitis, constipation, chronic cardiac failure, reflux oesophagitis, insomnia)	150 mg 229 days	Copper deficiency anaemia The patient had disuse syndrome following an operation for thoracoabdominal aortic aneurysm, experienced repeated aspiration pneumonia caused by dysphagia due to multiple cerebral infarction, received nutrition via gastric fistula, and was bedridden. approximately 7 months before administration Decreases in red blood cell (RBC) count and platelet (Plt) count were observed. Myelodysplastic syndrome was suspected, and the course was observed. Day 1 of administration As the patient had a history of gastric ulcer, administration of polaprezinc was started (75 mg twice daily). Administration of other concomitant medications including an enteral nutrition formulation was also started. Day 226 of administration A decrease in hemoglobin (Hb) to 5.3 g/dL was noted on blood tests, and thus severe anaemia was pointed out. White blood cell (WBC) count and Plt count also

				decreased. Myelodysplastic syndrome was also suspected, and the patient was referred to a hematologist and admitted for detailed examinations. Later, hematological tests showed the Cu level 7 μg/dL. Day 229 of administration (date of discontinuation) Copper deficiency anaemia was diagnosed, and as treatment, administration of an enteral nutrition supplement drink was started at 500 mL/day (400 kcal, containing Cu 4 mg and Zn 40 mg) to supplement Cu levels. Administration of polaprezinc was discontinued. 7 days after discontinuation As treatment, administration of Irradiated red cells concentrates - leukocytes reduced at 2 units was started (for 2 days). 17 days after discontinuation Hb increased to 7.7 g/dL, but atypical bone marrow cells were present and myelodysplastic syndrome could not be ruled out. The patient was transferred to this hospital for observation of the course of Copper deficiency and anaemia. At the time of hospital transfer, the Cu level was normal, 88 μg/dL. 31 days after discontinuation Hb, 7.8 g/dL; Cu, 143 μg/dL. 46 days after discontinuation Hb, 8.6 g/dL. 51 days after discontinuation Without blood transfusion, Hb and Cu levels were stable, and therefore it was determined that anaemia was recovering.
	Suspected concomitant drug: enteral nutrition formulation Concomitant medications: levodopa/carbidopa hydrate, isosorbide dinitrate, magnesium oxide, furosemide, aspirin dialuminate, pravastatin sodium, lansoprazole, brotizolam, tulobuterol			

Laboratory examination

	Day 132 of administration	Day 226 of administration	Day 229 of administration	17 days after discontinuation	31 days after discontinuation	46 days after discontinuation
RBC ($\times 10^4$/μL)	258	139	143	218	217	242
Hb (g/dL)	9.3	5.3	5.2	7.7	7.8	8.6
Ht (%)	27.8	16.8	17.7	22.9	23.9	27.3
WBC (/μL)	3280	1550	2270	3120	4140	3620
Plt ($\times 10^4$/μL)	6.8	6.5	8.4	6.8	6.6	6.0
Zn (μg/dL)	-	-	96	79	-	-
Cu (μg/dL)	-	7	11	88	143	-

2 Allopurinol

Brand name (name of company)	Zyloric Tablets 50 mg, 100 mg (GlaxoSmithKline K.K.), and the others
Therapeutic category	Gout preparations
Indications	Management of hyperuricemia in patients with gout or in hypertensive patients with hyperuricemia

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Drug-induced hypersensitivity syndrome (DIHS): Serious late-onset severe hypersensitivity symptoms may occur. Rash and/or pyrexia occur as initial symptoms, followed by lymphadenopathy, increased WBC count, increased eosinophil count, atypical lymphocytes, and organ damage such as hepatic function disorder. Among case reports associated with DIHS, there have been reports of cases developing type 1 diabetes mellitus (including fulminant type 1 diabetes mellitus) resulting in ketoacidosis. Patients should be carefully monitored. If any abnormalities are observed, the administration of this drug should be discontinued and appropriate measures should be adopted. The reactivation of viruses including Human Herpes Virus 6 (HHV-6) has been frequently found to be associated with DIHS. Even after the discontinuation of administration, symptoms, such as rash, pyrexia, and/or hepatic function disorder, may relapse or be prolonged, and symptoms of disorder in central nervous system such as encephalitis may occur. Therefore, patients should continue to be carefully monitored.

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 6 months (April 2013 to October 2016).
Cases related to type 1 diabetes mellitus associated with DIHS: 1 case (no fatal case)

The number of patients using the drug estimated by the MAH in the past 1 year: Approximately 2 300 000

Launched in Japan: July 2002 (Zyloric Tablets 50 mg)
January 1969 (Zyloric Tablets 100 mg)

Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
1	Female 70s	Hyperuricaemia (hypertension, osteoporosis, asthma, chronic cardiac failure)	300 mg Approximately 1 month	DIHS, fulminant type 1 diabetes mellitus Lifestyle history: no history of smoking, no history of drinking alcohol, no history of allergies Family history: none notable Day 1 of administration Administration of allopurinol was started. Approximately Month 1 of administration (date of hospitalization) General malaise, decreased appetite, and a bilateral femoral rash appeared. The rash was resolving, but decreased appetite and malaise were not, and the patient was admitted to the

				hospital for detailed investigation. At admission, a white coating of the buccal mucosa was present, and palpation of the neck found soft lymph nodes with good mobility 1 cm in size. Rash, joint swelling, and redness were absent. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) increased, blood urea nitrogen (BUN)/creatinine (Cr) increased, C-reactive protein (CRP) increased, and high blood digoxin concentration (2.53 ng/dL) were observed, but no increase in HbA1c was observed. Day 2 of hospitalization Food intake was good, and blood digoxin concentration, hepatic enzymes, and renal function were all tending to be resolving. The white coating in the oral cavity was suspected to be oral candida, and administration of fluconazole was started. Day 4 of hospitalization Pyrexia with a temperature ≥38°C appeared and appetite decreased. Renal function was impaired, and urine output also decreased. Fluid infusion did not increase urine output. There were no notable physical findings other than generalized lymphadenopathy. Day 6 of hospitalization As blood pressure decreased and urine output decreased, septic shock and organ failure were suspected. Blood culture samples were collected and administration of meropenem hydrate was started. Beta-D glucan was negative. Day 8 of hospitalization (date of discontinuation) Pyrexia did not resolve, and an erythematous rash appeared on the left forearm. Blood tests found WBC count 22 000/μL, atypical lymphocytes 14%, and BUN/Cr high. Blood culture tests (3 sets) were negative, cytomegalovirus antigen negative, Epstein-Barr virus viral capsid antigen (VCA) - immunoglobulin M (IgM) (−), VCA- immunoglobulin G (IgG) (+), anti- Epstein-Barr nuclear antigen antibody (+), HHV-6 IgM <10, IgG 1:20, soluble interleukin-2 receptor high (8620 U/mL). Lymph node ultrasound tests found enlarged cervical, axillary, and inguinal lymph nodes (maximum size 30 mm, lymph node hilum present), bone marrow aspiration found increases of a variety of atypical lymph cells, and a computed tomography scan from the chest to the pelvis found no obvious focus of infection. A drug eruption was suspected. All drugs were discontinued and prednisolone 20 mg was started. Subsequently, pyrexia resolved, the patient could take meals, and renal function was resolving. Spontaneous micturition was also achieved, but the rash on the left forearm spread to the trunk and face. 6 days after discontinuation Pyrexia was observed again. 8 days after discontinuation Lymph node biopsy and skin biopsy were performed. DIHS was suspected and steroid pulse therapy with methylprednisolone (1000 mg) for 3 days was started. The skin biopsy and lymph node biopsy found activation of T cells, but there were no findings of malignancy, and the results suggested a reaction to an event such as a virus infection. Pyrexia was resolved with steroid pulse therapy, and

				renal function also resolved. Subsequently, administration of prednisolone at 40mg/day was continued, and pyrexia, rash, and swollen lymph nodes were resolving, and atypical lymphocytes disappeared. And then, blood tests found an increase in HHV-6 IgG to 1:5120 (compared to 1:20 3 weeks earlier), and DIHS was diagnosed. 77 days after discontinuation The dosage of prednisolone was eventually tapered out to 12.5 mg, and the patient was discharged. 96 days after discontinuation Vomiting appeared. 97 days after discontinuation Consciousness disturbance appeared and the patient was transported to hospital as an emergency case. At the time of transportation, markedly increased blood glucose, acidemia, and increased ketone bodies were observed, and diabetes ketoacidosis was diagnosed. The patient was hospitalized. Tests at the time of admission found urine ketone positive, casual blood glucose level 1157 mg/dL, HbA1c 8.3%, and urinary C peptide 2.6 μg/day, meeting the diagnostic criteria for fulminant type 1 diabetes mellitus. Human leukocyte antigen (HLA) typing found HLA-A A24, A33, HLA-B B54, B58, HLA-DR DR4, DR14, HLA-DRB1*04:05-DQB1*04:01:01, DRB1*14:05:01-DQB1*05:03:01, and the former was thought to be a haplotype found with higher frequency in fulminant type 1 diabetes mellitus relative to healthy individuals. With continuous intravenous infusion of insulin, blood glucose levels stabilized, and eventually lispro insulin 50 mix was administered at 10-8-8 units by subcutaneous injection. 126 days after discontinuation The patient was transferred to a local medical institution. 132 days after discontinuation Pyrexia with a body temperature of 38°C was persisting. 139 days after discontinuation The patient was readmitted. After admission, seizures appeared, and spinal fluid tests found cell count 200/3 mm^3, spinal fluid glucose 63 mg/dL, spinal fluid adenosine deaminase 6.1 IU/L, and spinal fluid culture negative. Based on the results, viral meningoencephalitis was diagnosed, and the patient was intubated, tracheostomy was performed, and 2 months later, consciousness level were improving. Gastrostomy was performed, and the patient was extubated. After this, urinary tract infection, deep vein thrombosis, pseudomembranous enteritis, and exfoliative dermatitis of unknown cause developed, and management of the patient's general condition became difficult. 223 days after discontinuation The patient died.
	Concomitant medications: candesartan cilexetil, amlodipine besilate, montelukast sodium, alendronate sodium hydrate, metildigoxin, ethyl loflazepate, fluconazole, meropenem hydrate			

Laboratory examination

	Day 1 of hospitalization	Day 2 of hospitalization	Day 4 of hospitalization	Day 7 of hospitalization	Day 8 of hospitalization (date of discontinuation)	2 days after discontinuation	4 days after discontinuation
AST (IU/L)	155	125	68	22	14	14	-
ALT (IU/L)	190	165	112	39	34	25	-
BUN (mg/dL)	50	30	28	33	35	31	-
Cr (mg/dL)	1.59	1.01	1.07	2.09	1.97	1.23	-
CRP (mg/dL)	6.88	3.89	1.2	3.73	3.45	1.19	-
Urine output (mL/day)	-	-	400	200	-	-	4900
WBC (/μL)	8800	-	-	-	2 2000	-	-
Atypical lymphocytes (%)	3	-	-	-	14	-	-
Casual blood glucose (mg/dL)	130	-	-	-	-	-	-
HbA1c (%)	5.7	-	-	-	-	-	-
Urinary glucose	(-)	-	-	-	-	-	-
Urinary protein	(-)	-	-	-	-	-	-
Urinary occult blood	(-)	-	-	-	-	-	-
Urinary ketone	(-)	-	-	-	-	-	-

	6 days after discontinuation	7 days after discontinuation	8 days after discontinuation	10 days after discontinuation	69 days after discontinuation	87 days after discontinuation	97 days after discontinuation
AST (IU/L)	35	-	54	20	-	-	20
ALT (IU/L)	46	-	48	30	-	-	25
BUN (mg/dL)	16	-	18	21	-	-	73
Cr (mg/dL)	0.86	-	0.86	0.75	-	-	2.4
CRP (mg/dL)	0.64	-	0.54	0.79	-	-	0.34
Urine output (mL/day)	-	3600	-	-	-	-	-
WBC (/μL)	-	-	-	-	-	-	14 900
Atypical lymphocytes (%)	-	-	-	-	-	-	0
Casual blood glucose (mg/dL)	-	-	-	-	-	133	1157
Fasting blood glucose (mg/dL)	-	-	-	-	81	-	-
HbA1c (%)	-	-	-	-	5.6	-	8.3
GA (g/dL)	-	-	-	-	-	-	35.8
Immunoreactive insulin (IRI) (μU/L)	-	-	-	-	-	-	2.1
C-peptide immunoreactivity (CPR) (ng/dL)	-	-	-	-	-	-	1.1
Urinary glucose	-	-	-	-	-	-	(4+)
Urinary protein	-	-	-	-	-	-	(±)
Urinary occult blood	-	-	-	-	-	-	(2+)
Urinary ketone	-	-	-	-	-	-	(2+)
Urinary CPR (μg/day)	-	-	-	-	-	-	2.6
Urinary Alb (mg/day)	-	-	-	-	-	-	15.6

<Autoantibody related tests>
Anti-glutamic acid decarboxylase antibody: 2.4 U/mL (weak positive)
Anti-insulinoma antigen 2 antibody: 0.4 U/mL (negative)
Islet cell antibody: negative
Anti-IRI antibody: <0.4%

3 (a) Alogliptin benzoate
(b) Alogliptin benzoate/Pioglitazone hydrochloride
(c) Alogliptin benzoate/Metformin hydrochloride
(d) Teneligliptin hydrobromide hydrate
(e) Linagliptin

Brand name (name of company)	(a) Nesina Tablets 6.25 mg, 12.5 mg, 25 mg (Takeda Pharmaceutical Co., Ltd.) (b) Liovel Combination Tablets LD & HD (Takeda Pharmaceutical Co., Ltd.) (c) Inisync Combination Tablets (Takeda Pharmaceutical Co., Ltd.) (d) Tenelia Tablets 20 mg (Mitsubishi Tanabe Pharma Corporation) (e) Trazenta Tablets 5 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Therapeutic category	Antidiabetic agents
Indications	(a), (d), (e) Type 2 diabetes mellitus (b) Type 2 diabetes mellitus: To be used only when the concomitant use of alogliptin benzoate and pioglitazone hydrochloride is considered appropriate (c) Type 2 diabetes mellitus: To be used only when the concomitant use of alogliptin benzoate and metformin hydrochloride is considered appropriate

PRECAUTIONS (underlined parts are revised)

Adverse reactions (clinically significant adverse reactions)

Pemphigoid: Pemphigoid may occur. If blister, erosion or other signs and symptoms are observed, patients should be referred to a dermatologist, and appropriate measures such as the discontinuation of administration should be adopted.

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 5 months (April 2013 to September 2016).
Cases related to pemphigoid:
(a) 2 cases (no fatal case)
(b) 0 case
(c) Unapproved in Japan
(d) 7 cases (no fatal case)
(e) 10 cases (no fatal case)

The number of patients using the drug estimated by the MAH in the past 1 year:
(a) Approximately 510 000
(b) Approximately 140 000
(c) Unapproved in Japan
(d) Approximately 700 000
(e) Approximately 800 000

Launched in Japan:
(a) June 2010
(b) September 2011
(c) Unapproved in Japan
(d) September 2012
(e) September 2011

Nesina Tablets Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
1	Female 50s	Diabetes mellitus (hypertension)	25 mg 4 years and 1 month	Pemphigoid Day 1 of administration Administration of alogliptin benzoate was started. 1 year and 4 months of administration The patient was examined at A dermatology clinic due to a rash. 1 year and 9 months of administration After administration of oseltamivir phosphate, exacerbation of rash was noted. 1 year and 11 months of administration Toxicoderma was diagnosed at B dermatology clinic. 2 years and 1 month of administration Itching was diagnosed at C dermatology clinic. The patient was treated with phototherapy. Onset date (2 years and 5 months after the start of administration) Generalized itching appeared and multiple nodular rash lesions appeared over the whole body. 2 years and 8 months of administration Prurigo was diagnosed at B dermatology clinic and drugs including ointments were prescribed, but prurigo was not resolving. Later the patient visited C dermatology clinic and D dermatology clinic. The patient received treatment, but prurigo was not resolving. 3 years of administration The patient underwent skin biopsy at D dermatology clinic, and histology findings were consistent with pemphigoid. 3 years and 2 months of administration Due to suspected pemphigoid, the patient was referred from D dermatology clinic to E dermatology clinic. On the same day, tests were performed, and anti-bullous pemphigoid (BP) 180 antibody was 25.5 and anti-BP230 antibody was 32, both high levels. An indirect immunofluorescence (IIF) showed positive findings along the basal lamina, and nodular pemphigoid was diagnosed. The patient received outpatient treatment, mainly with steroid ointment, for 11 months, but pemphigoid was not resolving. Date of discontinuation (4 years 1 month of administration) Alogliptin benzoate were discontinued after the patient took the drug on the day. 1 week after discontinuation The patient was admitted to E dermatology clinic. After alogliptin benzoate were discontinued, the rash was recovering slightly. 16 days after discontinuation Liquid nitrogen therapy was started for nodules. 24 days after discontinuation Oral administration of prednisolone at 30 mg/day was started. 36 days after discontinuation Symptoms of nodular pemphigoid was resolving, and the

				patient was discharged.
	Concomitant medications: candesartan cilexetil, amlodipine besilate, oseltamivir phosphate			

Tenelia Tablets Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
2	Male 90s	Type 2 diabetes mellitus (stage 3 nephropathy)	40 mg 1 year and 11 months	Bullous pemphigoid (BP) Medical history: Hypertension As generalized itching appeared, symptomatic treatment was started, and treatment for diabetes mellitus was temporarily suspended. A skin biopsy showed no findings of pemphigoid, and prurigo was diagnosed. Oral treatment was given (including betamethasone/d-chlorpheniramine maleate combination drug) and the rash was recovering. Day 1 of administration Due to hyperglycaemia and dehydration, the patient was admitted to the internal medicine department of hospital A for treatment. Administration of linagliptin was started (40 mg/day). 4 month of administration The rash worsened (for the first time, blisters appeared and erythema appeared on the palms, the soles of the feet, and the fingers), and the patient was re-examined at hospital A. BP appeared. 1 year and 1 month of administration As the condition was resistant to treatment, the patient was examined at the dermatology department of hospital B. Anti-BP180 antibody 8.1 (U/mL). The patient was hospitalized to start steroid treatment. Prednisolone 20mg/day was administered orally for 15 days. <Biopsy findings> There was no epidermal change. The formation of blisters separating from the dermis immediately beneath the epidermis was observed. This was accompanied by marked neutrophil and eosinophil infiltration inside and on the epidermal side of the blisters. Inflammatory cell infiltration, mainly by eosinophils, was also observed in the periphery of blood vessels in the superficial dermis. There was no obvious hyperkeratosis, acanthosis, or increase in collagen fiber in the dermis. Findings were consistent with BP. Since then, prednisolone was tapered out, to 15 mg/day (21 days), 12.5 mg/day (28 days), 10 mg/day (56 days), 8 mg/day (91 days), and 7.5 mg/day. 1 year and 3 month of administration Anti-BP180 antibody 4.7 (U/mL). 1 year and 11 month of administration (date of discontinuation) During administration of prednisolone at 7.5 mg, linagliptin was discontinued. Before discontinuation of linagliptin, itching and redness were present, and it was necessary to apply steroid ointment on consecutive days, but after linagliptin was discontinued, itching disappeared in a few days, and symptoms were tolerable without the application of

				ointment. Redness remained but seemed to be fading. Anti-BP180 antibody <3.0 (U/mL). 28 days after discontinuation BP was recovering.
	Concomitant medications: olopatadine hydrochloride, sennoside, magnesium oxide			

Trazenta Tablets Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and Therapeutic measures
3	Male 40s	Type 2 diabetes mellitus (hypertension, dyslipidaemia, chronic kidney disease, diabetic retinopathy)	5 mg Approximately 12 months	Pemphigoid Day 1 of administration Administration of linagliptin was started. Approximately 10 months of administration BP appeared. Tense bullae appeared on the face, the front of the chest, and the lower limbs. Approximately 11 months of administration From a skin biopsy, BP was diagnosed. Findings: Subepidermal bullae containing eosinophils were observed. In the lower epidermis, inflammatory cell infiltration mixed with eosinophils was present. IIF: epidermal basal lamina IgG C3, positive Treatment with prednisolone 5 mg/day, mizoribine 100 mg/day, nicotinamide 600 mg/day, and minocycline hydrochloride 200 mg/day was started, but new blisters continued to appear. Approximately 12 months of administration (date of discontinuation) Linagliptin was discontinued. 24 days after discontinuation The patient was admitted to a dermatology clinic. Desquamation and blisters: present on the face, trunk, and bilaterally on the lower limbs and thighs. Pyrexia, papuloerythematous rash, erythema multiforme type rash, erythroderma, swollen lymph nodes, oedema, papule, rubedo: absent. Administration of insulin was started for diabetes mellitus. 69 days after discontinuation Skin symptoms seemed to be resolving and the patient was discharged. 104 days after discontinuation Treatment with prednisolone at 5 mg/day was continuing. 153 days after discontinuation Pemphigoid resolved.
	Concomitant medications: olmesartan medoxomil, ezetimibe, nifedipine			

Laboratory examination

	Date of discontinuation	63 days after discontinuation	104 days after discontinuation
HbA1c (%)	8.1	-	7.1
WBC (cells/μL)	8900	-	7000
CRP (mg/dL)	0.30	-	-
IgG (mg/dL)	-	-	948
Drug lymphocyte stimulation test	-	Negative	-

5

Revision of Precautions (No. 280)

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 22 and 25, 2016.

1

Local Antimicrobial agents

Formalin

Brand name	Formalin Kenei (Kenei Pharmaceutical Co., Ltd.), Formalin Kozakai M (Kozakai Pharmaceutical Co., Ltd.), Junsei Formalin (Junsei Yakuhin Kogyo), Formalin Tatsumi M (Tatsumi Yakuhin Kogyo), Formalin Taisei (Taisei Yakuhin Kogyo), Formalin Tokai (Tokai Seiyaku), Formalin Yamazen (Yamazen Pharmaceutical Co., Ltd.), Formalinum Ebisu (Ebisu Yakuhin Kako Corporate), Formalin Nikko (Nikko Pharmaceutical Co., Ltd.)
Contraindications	When used in the dentistry field: Patients with a history of hypersensitivity to any of the ingredients of this product
Adverse reactions (clinically significant adverse reactions)	When used in the dentistry field: Shock and anaphylaxis: shock or anaphylaxis may occur. Patients should be carefully monitored. If any abnormalities such as urticaria, pruritus, dyspnoea, and decreased blood pressure are observed, appropriate measures should be adopted.

2

Analgesics and sedatives for dental preparations / Pulp capping agents

(a) Formalin/Guaiacol
(b) Formalin/Cresol
(c) Cresol/Formalin/Clove oil/Zinc oxide mixt

Brand name	(a) Formalin Guaiacol FG Neo (Neo Dental Chemical Products Co., Ltd.) (b) Clear FC (Agsa Japan Co., Ltd.), Formocresol Dental Disinfectants “Showa” (Showa Yakuhin Kako Co., Ltd.), Formcresol FC Neo (Neo Dental Chemical Products Co., Ltd), Dental Formcresol Murakami (Agsa Japan Co., Ltd.), Dental Formalin Cresol (Nippon Shika Yakuhin Co., Ltd.) (c) Palpack V (Nippon Shika Yakuhin Co., Ltd.)
Contraindications	Patients with a history of hypersensitivity to any of the ingredients of this product
Adverse reactions (clinically significant adverse reactions)	Shock and anaphylaxis: shock or anaphylaxis may occur. Patients should be carefully monitored. If any abnormalities such as urticaria, pruritus, dyspnoea, and decreased blood pressure are observed, appropriate measures should be adopted.

3 **Miscellaneous metabolism agents-Miscellaneous**

Zoledronic acid hydrate

Brand name

(1) Zometa for I.V. Infusion 4 mg/5 mL, 4 mg/100 mL (Novartis Pharma K.K.), and the others

(2) Reclast for I.V. Infusion 5 mg (Asahi Kasei Pharma Corporation)

Adverse reactions (clinically significant adverse reactions)

Acute renal failure, interstitial nephritis, Fanconi syndrome: renal disorders such as acute renal failure, interstitial nephritis, and Fanconi syndrome (Proximal kidney tubule injury may cause hypophosphataemia, hypokalaemia, metabolic acidosis etc.) may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as the discontinuation of administration should be adopted.

4 **Antivirals**

Famciclovir

Brand name

Famvir Tablets 250 mg (Asahi Kasei Pharma Corporation)

Adverse reactions (clinically significant adverse reactions)

Shock and anaphylaxis: shock or anaphylaxis may occur. Patients should be carefully monitored. If any abnormalities such as urticaria, decreased blood pressure, and dyspnoea are observed, the administration of this drug should be discontinued and appropriate measures should be adopted.

5 **Psychotropics**

(a) Duloxetine hydrochloride
(b) Venlafaxine hydrochloride
(c) Milnacipran hydrochloride

Brand name

(a) Cymbalta Capsule 20 mg, 30 mg (Shionogi & Co., Ltd.)
(b) Effexor SR Capsule 37.5 mg, 75 mg (Pfizer Japan Inc.)
(c) Toledomin Tablet 12.5 mg, 15 mg, 25 mg, and 50 mg (Asahi Kasei Pharma Corporation), and others

Important Precautions

As symptoms such as somnolence and dizziness may occur, caution patients about operating hazardous machine such as driving a car. Patients should also be instructed that, if they experience these symptoms, they should not be engaged in hazardous machine operation such as driving a car.

6

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 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, 2016)
◎: Products for which EPPV was initiated after November 1, 2016

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	Albutrepenonacog Alfa (Genetical Recombination) Idelvion I.V. Injection 250, 500, 1000, 2000	CSL Behring K.K.	November 29, 2016
◎	Rifaximin Rifxima Tablets 200 mg	Aska Pharmaceutical. Co., Ltd.	November 29, 2016
◎	Budesonide Zentacort Capsules 3 mg	Zeria Pharmaceutical Co., Ltd.	November 29, 2016
◎	Alogliptin Benzoate/Metformin Hydrochloride Inisync Combination Tablets	Takeda Pharmaceutical Company Limited	November 29, 2016
◎	Zoledronic Acid Hydrate Reclast for I.V. Injection 5 mg	Asahi Kasei Pharma Corporation	November 25, 2016
◎	Ponatinib Hydrochloride Iclusig Tablets 15 mg	Otsuka Pharmaceutical Co., Ltd.	November 21, 2016
◎	Selexipag Uptravi Tablets 0.2 mg, 0.4 mg	Nippon Shinyaku Co., Ltd.	November 21, 2016
◎	Ixekizumab (Genetical Recombination) Taltz 80 mg Syringe for SC Injection, Taltz 80 mg Auto-Injector for SC Injection	Eli Lilly Japan K.K.	November 21, 2016
◎	Grazoprevir Hydrate Grazyna Tablets 50 mg	MSD K.K.	November 18, 2016
◎	Elbasvir Erelsa Tablets 50mg	MSD K.K.	November 18, 2016
◎	Elotuzumab (Genetical Recombination) Empliciti I.V. Injection 300 mg, 400 mg	Bristol-Myers Squibb K.K.	November 18, 2016
◎	Bilastine Bilanoa Tablets 20 mg	Taiho Pharmaceutical Co., Ltd.	November 18, 2016
◎	Telmisartan/Amlodipine Besilate/ Hydrochlorothiazide Micatrio Combination Tablets	Nippon Boehringer Ingelheim Co., Ltd.	November 18, 2016
◎	Idarucizumab (Genetical Recombination) Prizbind Intravenous Solution 2.5 g	Nippon Boehringer Ingelheim Co., Ltd.	November 18, 2016
◎	Desloratadine Desalex Tablets 5 mg	MSD K.K.	November 18, 2016

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
◎	Adapalene/Benzoyl Peroxide Epiduo Gel	Galderma S.A.	November 4, 2016
	Brodalumab (Genetical Recombination) Lumicef Subcutaneous Injection 210 mg Syringe	Kyowa Hakko Kirin Co., Ltd.	September 30, 2016
	Adalimumab (Genetical Recombination) Humira for SC Injection 40 mg syringe 0.8 mL, 40 mg syringe 0.4 mL, 80 mg syringe 0.8 mL[*1]	AbbVie GK	September 28, 2016
	Aripiprazole Abilify Tablets 1 mg, 3 mg, 6 mg, 12 mg, OD Tablets 3 mg, 6 mg, 12 mg, powder 1%, oral solution 0.1%[*2]	Otsuka Pharmaceutical Co., Ltd.	September 28, 2016
	Propranolol Hydrochloride Hemangiol Syrup for Pediatric 0.375%[*3]	Maruho Co., Ltd.	September 16, 2016
	Progesterone OneCrinone 90 mg Progesterone Vaginal Gel	Merck Serono Co., Ltd.	September 7, 2016
	Alirocumab (Genetical Recombination) Praluent Subcutaneous Injection pen 75 mg, 150 mg, Syringe 75 mg, 150 mg	Sanofi K.K.	September 5, 2016
	Levodopa/Carbidopa Hydrate Duodopa enteral combination solution	AbbVie GK	September 1, 2016
	Lacosamide Vimpat Tablets 50 mg, 100 mg	UCB Japan Co. Ltd.	August 31, 2016
	Sodium Picosulfate Hydrate, Magnesium Oxide, Anhydrous Citric Acid Picoprep Combination Powder	Ferring Pharmaceuticals Co., Ltd.	August 31, 2016
	Carfilzomib Kyprolis Intravenous Infusions 10 mg, 40 mg	ONO Pharmaceutical Co., Ltd.	August 31, 2016
	Nivolumab (Genetical Recombination) Opdivo Intravenous Infusions 20 mg, 100 mg[*4]	ONO Pharmaceutical Co., Ltd.	August 26, 2016
	Remifentanil Hydrochloride Ultiva Intravenous 2 mg, 5 mg[*5]	Janssen Pharmaceutical K.K.	August 26, 2016
	Vigabatrin Sabril 500mg Powder	Sanofi K.K.	July 27, 2016
	Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide Fumarate Genvoya Combination Tablets	Japan Tobacco Inc.	July 8, 2016
	Octocog Beta (Genetical Recombination) Kovaltry for iv injection 250, 500, 1000, 2000, 3000	Bayer Yakuhin, Ltd.	June 29, 2016
	Bexarotene Targretin Capsules 75 mg	Minophagen Pharmaceutical Co., Ltd.	June 23, 2016
	Maxacalcitol/betamethasone butyrate propionate Marduox Ointment	Chugai Pharmaceutical Co., Ltd.	June 21, 2016
	Primaquine Phosphate Primaquine Tablets 15 mg	Sanofi K.K.	June 17, 2016
	Dutasteride (1) Zagallo Capsules 0.1 mg (2) Zagallo Capsules 0.5 mg	GlaxoSmithKline K.K.	June 13, 2016
	Mepolizumab (Genetical Recombination)	GlaxoSmithKline K.K.	June 7, 2016

	Nonproprietary name Brand name on	Name of the MAH	Date of EPPV initiate
	Nucala for Subcutaneous Injection 100 mg		
	Radium (^{223}Ra) Chloride Xofigo Injection	Bayer Yakuhin, Ltd.	June 1, 2016
	Rurioctocog Alfa Pegol (Genetical Recombination) Adynovate Intravenous 250, 500, 1000, 2000	Baxalta Japan Ltd.	June 1, 2016
	Trametinib Dimethyl Sulfoxide Mekinist Tablets 0.5mg, 2mg	Novartis Pharma K.K.	June 1, 2016
	Dabrafenib Mesilate Tafinlar Capsules 50mg, 75mg	Novartis Pharma K.K.	June 1, 2016

*1 Non-infectious intermediate, posterior and panuveitis
*2 Irritability associated with autism spectrum disorder in childhood
*3 Infantile haemangioma
*4 Radically unresectable or metastatic renal cell carcinoma
*5 Analgesia in maintaining general anesthesia of children