Pharmaceuticals and Medical Devices Safety Information

No. 284 October 2011

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

Published by
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Translated by
Pharmaceuticals and Medical Devices Agency

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No. 284 October 2011

Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare, Japan

[Outline of Information]

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3	**Summary of Report on Adverse Reactions to the Influenza A (H1N1) Vaccine in the 2010 Season**		A joint meeting of the Subcommittee on Drug Safety of Committee on Drug Safety and the Influenza A (H1N1) Vaccine Adverse Reaction Review Committee was held on July 13, 2011, and a summary of adverse reactions to the influenza A (H1N1) vaccines that occurred up until May 31, 2011 was reported. In addition, after organizing and reviewing the adverse reactions to the influenza vaccines, which have been collected up to March 31, 2011, MHLW issued a notification on August 9, 2011 and required marketing authorization holders to revise the Precautions section of package inserts. The details of the safety measures are also presented in this section.	12

4	**Important Safety Information**	*P* *C*	Voriconazole: Regarding the revision of the Precautions section of package inserts of drugs in accordance with the Notification dated September 20, 2011, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.	18
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D: Distribution of Dear Healthcare Professional Letters *P*: Revision of Precautions *C*: Case Reports

PMDA medi-navi (Pharmaceuticals and Medical Devices Information E-mail Alert Service)

The PMDA is providing the "PMDA medi-navi" a Pharmaceuticals and Medical Devices Information E-mail Alert Service (only available in Japanese language), when important safety information regarding pharmaceuticals and medical devices including Dear Healthcare Professional Letters or Revision of Precautions is issued. This e-mail service will enable you to obtain safety information faster and more efficiently, free of charge. Please feel free to use this service for your faster information collection.
See our website for details of the service. → http://www.info.pmda.go.jp/info/idx-push.html

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

ADRs	Adverse drug reactions
ALT (GPT)	Alanine aminotransferase (Glutamate pyruvate transaminase)
AST (GOT)	Aspartate aminotransferase (Glutamate oxaloacetate transaminase)
CRP	C-reactive protein
CT	Computed tomography
DLST	Drug lymphocyte stimulation test
eGFR	estimated glomerular filtration rate
EPPV	Early Post-marketing Phase Vigilance
HA	Haemagglutinin
HLA-A*3101	Human leukocyte antigens-A*3101
HLA-B*1502	Human leukocyte antigens-B*1502
HLT	High Level Terms
IU	International unit
KL-6	Sialylated carbohydrate antigen KL-6 (Krebs von den Lunge-6)
LDH	Lactate dehydrogenase
MAH	Marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
NSF	Nephrogenic Systemic Fibrosis
PMDSI	Pharmaceuticals and Medical Devices Safety Information
PT	Preferred Terms
WBC	White blood cell count

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Safety Measures against Disturbed Consciousness Associated with the Use of Smoking Cessation Aid CHAMPIX Tablets

Active ingredient Brand Name (name of company)	Active ingredient	Brand Name (name of company)
	Varenicline tartrate	CHAMPIX Tablets 0.5 mg, 1 mg (Pfizer Japan Inc.)
Therapeutic Category	Non-main therapeutic purpose agents-Miscellaneous	
Indications	Aid to smoking cessation in nicotine-dependent smokers	

1. Introduction

Varenicline tartrate is an agonist and antagonist of the $\alpha_4\beta_2$ nicotine receptor in the brain. CHAMPIX Tablets (hereinafter referred to as "CHAMPIX") were approved as an aid to smoking cessation in nicotine-dependent smokers in Japan in January 2008. The accumulated number of users of this drug is approximately 850,000 (data from May 2008 to June 2011, estimated by MAH).

An alert for dizziness and somnolence associated with CHAMPIX has been included in the "Important Precautions" and "Other Adverse Reactions" in the package insert since the product's launch. In the post-marketing setting, cases of disturbed consciousness (e.g., decreased level of consciousness and loss of consciousness), some of which resulted in automobile accidents, have been reported among CHAMPIX users. Based on the above, safety measures against disturbed consciousness and associated automobile accidents were reviewed, and MHLW issued a notification in July 2011 and required the MAH of CHAMPIX to revise the package insert to emphasize alerts for the users to refrain from engaging in potentially hazardous machine operations including driving.

However, automobile accidents involving CHAMPIX users were still reported after the revision of package insert. The CHAMPIX users should be more thoroughly informed to refrain from engaging in potentially hazardous machine operation including driving after taking the drug. Accordingly, MHLW required the MAH of CHAMPIX to take additional safety measures, and PMDA has been providing information to healthcare professionals and the drug users to promote proper use of CHAMPIX. The background and details of the safety measures are provided below.

2. Review of the adverse reaction reports in Japan and the safety measures

The PMDA received 16 cases of disturbed consciousness [Note)] associated with CHAMPIX in Japan by April 21, 2011, 3 cases of which occurred while driving. After evaluation of the 16 cases, the causality between CHAMPIX and disturbed consciousness could not be ruled out in 6 cases. The causality between CHAMPIX and disturbed consciousness could not be ruled out in all 3 cases that occurred while driving (Table). Of the 3 cases there was a case in which a patient suddenly lost consciousness without prodrome, and another case in which a patient lost consciousness while driving and caused an accident.

Note) For the tabulation of adverse reactions, Preferred Terms (PTs) under the High Level Term (HLT) "Disturbances in consciousness NEC" listed in the MedDRA version 14.1 were used.

Table: Reports of disturbed consciousness [May 8, 2008 (initial launch) to April 21, 2011]

Adverse reaction report	Number of cases
Disturbed consciousness	16 (6)
Disturbed consciousness that occurred while driving in the above cases	3 (3)

* Bracketed number indicates cases in which the PMDA considered the causality between CHAMPIX and disturbed consciousness could not be ruled out.

Based on the review of the adverse reaction reports, alerts against disturbed consciousness were considered necessary. MHLW issued a notification on July 5, 2011 and required the MAH to revise the "Precautions" in the package insert as follows (underlined parts are revised). The MAH was also required to prepare a patient instruction brochure to be used by physicians and pharmacists to alert CHAMPIX users about restrictions on engaging in potentially hazardous machine operations including driving.

Important Precautions	Some cases of dizziness, somnolence, and disturbed consciousness leading to automobile accident have been reported. Patients should be advised to refrain from engaging in potentially hazardous machine operations including driving.
Adverse Reactions (clinically significant adverse reactions)	**Disturbed consciousness**: Disturbed consciousness including decreased level of consciousness and loss of consciousness may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

3. Adverse reactions reported after the revision of package insert and safety measures hereafter

After the notification was issued about revision of the package insert on July 5, 2011, the MAH distributed Information on Revision of Precautions and patient instruction brochures to medical institutions to provide healthcare professionals and CHAMPIX users with relevant information. However, 12 cases of disturbed consciousness (including cases that occurred before the package insert revision) have been reported as adverse reactions between issuance of the notification and September 30, 2011. Nine of them experienced disturbed consciousness while driving and caused accidents, including 6 cases that occurred after issuance of the notification. These cases included cases in which the patient had been advised against driving by their physicians. Accordingly, PMDA requested the MAH of CHAMPIX to strengthen the information provision to healthcare professionals about potentially hazardous machine operations including driving and to consider further safety measures to ensure thorough communication between healthcare professionals and CHAMPIX users. PMDA posted a "Request for Proper Use of Drugs" on its website to alert healthcare professionals and CHAMPIX users against potentially hazardous machine operations including driving.

Healthcare professionals are encouraged to ensure that thorough instructions are given to CHAMPIX users and to obtain their understanding to refrain from engaging in potentially hazardous machine operations including driving.

4. Case summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 60s	Smoking cessation therapy (chronic obstructive pulmonary disease, bullous lung disease)	0.5 mg for 3 days ↓ 1 mg for 4 days ↓ 2 mg for 1 day	**Loss of consciousness, tremor, salivary hypersecretion** Smoking status: details unknown 10 years before administration: The patient was cured of bullous lung disease in the left lung. 4 months before administration: The patient developed chronic obstructive pulmonary disease. Administration of tiotropium bromide hydrate was started. Day 1 of administration: Administration of varenicline tartrate 0.5 mg/day was started for smoking cessation therapy. Day 4 of administration: The dose of varenicline tartrate was increased to 1 mg/day. The patient had no symptoms. Administration of varenicline tartrate was continued. Day 8 of administration (day of discontinuation): The dose of varenicline tartrate was increased to 2 mg/day. The patient took varenicline tartrate 1 mg after breakfast. About 20 minutes later, the patient had salivation, tremulousness in the whole body, and loss of consciousness while driving. When the patient came to, the car was in a roadside ditch. The patient took varenicline tartrate 1 mg after dinner. About 20 minutes later, the patient had salivation, tremulousness in the whole body, and loss of consciousness while driving again. He almost drove into an electric pole. The symptoms improved without treatment. Administration of varenicline tartrate was discontinued. The patient has never had these symptoms again.
	Concomitant medications: tiotropium bromide hydrate			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 60s	Smoking cessation therapy (asthma, otitis media, chronic sinusitis, essential tremor, drug hypersensitivity)	0.5 mg for 3 days ↓ 1 mg for 6 days ↓ 2 mg for 24 days ↓ (no treatment for 3 days) ↓ 2 mg for 56 days	**Illusion, altered state of consciousness, road traffic accident** Number of cigarettes: 15 cigarettes/day; Smoking history: 40 years Day 1 of administration: The patient started receiving varenicline tartrate 0.5 mg/day for the treatment of nicotine dependence. Day 4 of administration: The dose of varenicline tartrate was increased to 1 mg/day. Day 10 of administration: The dose of varenicline tartrate was increased to 2 mg/day. Day 29 of administration (day of onset): While driving, the patient suddenly had unusual vision, and the crossing in front started to turn round. He subsequently lost visual perception and drove over the left curve. He temporarily lost consciousness and memory. He felt fuzzy. After resting for a while he went home. Day 30 of administration: Cranial CT showed no abnormality. Intravenous drip infusion

				was performed. Day 31 of administration: The patient had symptoms of a common cold such as slight fever (37.4°C), nausea, and queasiness secondary to summer lethargy. Intravenous drip infusion was performed. Day 34 of administration (day of discontinuation): Administration of varenicline tartrate was discontinued. Day of readministration: Administration of varenicline tartrate 2 mg/day was resumed. Day 56 of readministration (day of termination): Administration of varenicline tartrate was completed. The patient was advised to drive carefully and has never had an accident again.
	Concomitant medications: none			

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The Guidelines for Provision of Dear Healthcare Professional Letters of Emergent/Rapid Safety Communications

1. Introduction

To prevent health hazards associated with the use of drugs and medical devices, it is important that post-marketing reports of adverse reactions and defects be collected and reviewed in order to promptly provide feedback about necessary information to medical institutions.

According to Article 77-4 of the Pharmaceutical Affairs Law (Law No. 145, 1960), when MAHs of drugs or medical devices learn that the use of drugs or medical devices that they have marketed might cause onset or spread of hazards to public health or hygiene, necessary measures shall be taken, including recall, suspension of sales, and information provision to prevent such hazards. Information has been provided through not only the Information on Revision of Precautions, but through Dear Healthcare Professional Letters of Emergent Safety Communications (Yellow Letter), containing emergent and important safety information about drugs and medical devices, or Dear Healthcare Professional Letters of Rapid Safety Communications (Blue Letter), containing information that does not require emergent communications but should be promptly provided to alert healthcare professionals.

The circumstances of provision of the important safety information have significantly changed. For example, PMDA has issued the PMDA medi-navi, Pharmaceuticals and Medical Devices Information E-mail Alert Service, to improve accessibility of safety information of drugs and medical devices, and easy-to-understand information is expected for not only healthcare professionals but also the general public. Based on the above, guidelines for Provision of Dear Healthcare Professional Letters of Emergent/Rapid Safety Communications were developed. Details are described below.

2. Guidelines for preparation of Dear Healthcare Professional Letters of Emergent Safety Communications and Dear Healthcare Professional Letters of Rapid Safety Communications

Other than “Information on Revision of Precautions,” the drug and medical device safety information is provided in the form of Dear Healthcare Professional Letters of Emergent Safety Communications (Yellow Letter) and Dear Healthcare Professional Letters of Rapid Safety Communications (Blue Letter) taking into consideration the occurrence of clinically significant adverse reactions and product defects and safety measures taken by overseas regulatory authorities, as listed in list (1). The Dear Healthcare Professional Letters are issued according to the urgency of the situation when certain safety measures listed in list (2) become necessary in order to provide information more promptly to medical institutions.

(1) Situations taken into consideration when preparing Dear Healthcare Professional Letters of Emergent Safety Communications

- Occurrence of deaths, disabilities, events that may result in death or disability, or untreatable diseases associated with adverse reactions or medical device defects, as directed by Article 77-4-2 of the Pharmaceutical Affairs Law

- Newly identified safety concerns including an unknown and serious adverse reaction or medical device defect, which outweighs the therapeutic efficacy
- Emergent and significant safety measures taken by overseas regulatory authorities
- Safety concerns that have not been effectively resolved by issuance of Dear Healthcare Professional Letters of Emergent Safety Communications or Dear Healthcare Professional Letters of Rapid Safety Communications

(2) Measures taken when preparing Dear Healthcare Professional Letters of Emergent Safety Communications

- Addition of new Warnings section or warning sentences
- Addition of new Contraindications section or contraindication sentences
- Revision of Precautions requiring implementation of new safety measures (e.g., performing examinations)
- Revision of Indications, Dosage and Administration, and/or Instruction for Use due to safety reasons
- Regulatory measures including product recall (discontinuation, suspension, or withdrawal of approval) taken due to safety reasons
- Other specific measures for prevention and/or early detection of the adverse reaction

When an emergent and significant alert to medical professionals or appropriate measures (ex. restriction on the use of a drug/medical device) are required, the MAH is to issue Dear Healthcare Professional Letters of Emergent Safety Communications to healthcare professionals as well as to the general public including patients who use the drug/medical device.

The so-called Blue Letter, or safety information printed in blue paper, is now called Dear Healthcare Professional Letters of Rapid Safety Communications. The Dear Healthcare Professional Letters of Rapid Safety Communications will be distributed by the MAH as a means to communicate important information almost equivalent to the Dear Healthcare Professional Letters of Emergent Safety Communications when an alert needs to be issued to healthcare professionals in a faster manner than the conventional Information on Revision of Precautions or when certain measures to ensure proper drug/medical device use need to be notified. The information will be provided to the general public as necessary based on the usage of the drug/medical device.

3. Information provision

When Dear Healthcare Professional Letters of Emergent/Rapid Safety Communications is issued, the MAH is to post the relevant information on the PMDA website (http://www.info.pmda.go.jp/kinkyu_anzen/kinkyu_index.html) as well as on its company website to ensure prompt and exhaustive information provision. The information will be simultaneously distributed to the subscribers to the PMDA medi-navi. In addition, the information is to be directly provided to the medical institutions , pharmacies and other facilities where the product is delivered via information brochures distributed by medical representatives, direct mail, fax and/or e-mail within 1 month.

After Dear Healthcare Professional Letters of Emergent Safety Communications are distributed, the MAH and the regulatory authorities are to issue a separate press release based on the significance and urgency of the situation. When the general public is directly involved in the safety measures (e.g., when the product is recalled), the MAH is to publish an announcement in newspapers.

4. Request for healthcare professionals

Dear Healthcare Professional Letters of Emergent Safety Communications and Dear Healthcare

Professional Letters of Rapid Safety Communications are important media for prompt communication of especially significant and urgent drug/medical device safety information. When these messages are issued, medical institutions, pharmacies and other facilities are advised to read the information and share it among healthcare professional staff members in a prompt manner.

As described in Section 3, Dear Healthcare Professional Letters of Emergent/Rapid Safety Communications will be promptly distributed to the subscribers to the PMDA medi-navi via e-mail, which is the fastest means of communication. The PMDA medi-navi also distributes information concerning Information on Revision of Precautions, Class I recall of drug/medical device (recall of a product that may cause serious health hazards or deaths), and medical safety information in a prompt manner. [See PMDSI No. 278 (March 2011) for details.] Although the number of subscribers is graduatly increasing, there are still several medical institutions and pharmacies which have no subscribers to the PMDA medi-navi. They are encouraged to register PMDA medi-navi (free of charge) as soon as possible to obtain Dear Healthcare Professional Letters of Emergent/Rapid Safety Communications and take necessary safety measures accordingly. As an additional function of the PMDA medi-navi, My Drug List for Safety Update has been provided since June 2011. Users can register drugs of interest and browse the latest package inserts and interview forms of the drugs and Dear Healthcare Professional Letters of Emergent Safety Communications issued to date anytime. Your registration to the PMDA medi-navi and use of the services is highly encouraged to further improve drug and medical device safety measures.

<References> (including provisionally translated titles)

Pharmaceuticals and Medical Devices Information E-Mail Alert Service (PMDA medi-navi) (only available in Japanese language)
http://www.info.pmda.go.jp/info/idx-push.html

My Drug List for Safety Update (only available in Japanese language)
http://www.info.pmda.go.jp/info/idx-myiyaku.html

Dear Healthcare Professional Letters of Emergent Safety Communications (Yellow Letter) and Dear Healthcare Professional Letters of Rapid Safety Communications (Blue Letter) (only available in Japanese language)
http://www.info.pmda.go.jp/kinkyu_anzen/kinkyu_index.html

PMDA Alert for Proper Use of Drugs (only available in Japanese language)
http://www.info.pmda.go.jp/iyaku_info/tekisei_pmda.html

PMDA Medical Safety Information
http://www.info.pmda.go.jp/anzen_pmda/iryo_anzen.html

3

Summary of Report on Adverse Reactions to the Influenza A (H1N1) Vaccine in the 2010 Season

1. Introduction

Influenza A (H1N1) (now called the 2009 influenza (H1N1)) vaccines were provided to respond to the 2009 influenza pandemic as a part of the national vaccination program in accordance with the Operating Procedure for Influenza A (H1N1) Vaccination at the Contract Medical Institutions (Vaccination Operating Procedure) (*HSB Notification No. 1013-4, by the Vice Minister of Health Service Bureau, MHLW, dated October 13, 2009).

In the 2010 season, vaccination with trivalent influenza vaccine (including 2009 influenza [H1N1] and seasonal influenza A/H3N2 and B) was started in October 2010. Adverse reactions which met the Adverse Reaction Reporting Criteria were directly reported to the MHLW in accordance with the Vaccination Operating Procedure, regardless of causality as in the 2009 season. The casualty assessments of the reported adverse reactions have been reviewed by the PMDA when necessary. Death and serious cases have been investigated and discussed based on opinions from experts at the joint meeting of the Subcommittee on Drug Safety of Committee on Drug Safety and the Influenza A (H1N1) Vaccine Adverse Reaction Review Committee, which examined the necessity of safety measures.

The 2010 season summary of adverse reactions associated with the influenza vaccines, which were reported up to May 31, 2011, is presented below.

In addition, adverse reactions associated with the influenza vaccines, which had been collected up to March 31, 2011, were identified and reviewed. These adverse reactions were reviewed to determine whether an alert requiring a package insert revision should be issued. Details of the safety measures are also presented.

*Provisional Translation: HSB Notification No. 1013-4, by the Vice Minister of Health Service Bureau, MHLW, dated October 13, 2009

2. Adverse reactions to the influenza A (H1N1) vaccines reported in accordance with the Operating Procedure for Influenza A (H1N1) Vaccination at Contract Medical Institutions (October 1, 2010 to May 31, 2011)

(1) Number of reported adverse reactions and reporting frequency

Table 1 shows the number of reported 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 the medical institutions.

Table 1 Number of reported adverse reactions and reporting frequency

	Adverse reactions reported by medical institutions			Adverse reactions reported by MAHs* (Serious adverse reaction report)	
Estimated number of vaccinated persons (number of vaccination)	Reported number of adverse reactions (reporting frequency)	Number of reported serious cases (reporting frequency)	Number of reported deaths (reporting frequency)	Number of reported serious cases (reporting frequency)	Number of reported deaths (reporting frequency)
49,460,846 (as of March 31, 2011)	673 (0.001%)	129 (0.0003%)	16 (0.00003%)	97 (0.0002%)	6 (0.00001%)

[unit: case]

* The adverse reactions reported by MAHs were determined serious in accordance with the Pharmaceutical Affairs Law Article 77-4-2 and may overlap some other cases of adverse reaction reports by the medical institutions.

(2) Outline of adverse reactions reported by sex, age group, and underlying disease

Number of reported adverse reactions to the influenza vaccine are shown by sex and age group in Tables 2 and 3, respectively.

Table 2 Number of reports by sex

Sex	Number of adverse reactions reported by medical institutions	Number of adverse reactions reported by MAHs
Male	280	35
Female	391 (3 pregnant women)	60
Unknown	2	2
Total	673	97

Table 3 Number of reports by age

Age	Adverse reactions reported by medical institutions			Number of adverse reactions reported by MAHs	
	Reported number of adverse reactions	Number of serious adverse reactions	Number of reported deaths	Number of serious adverse reactions	Number of reported deaths
0 to 9	193	26	1	28	0
10 to 19	53	13	0	12	0
20 to 29	62	10	0	2	0
30 to 39	82	14	0	4	0
40 to 49	55	6	0	6	0
50 to 59	46	9	1	6	1
60 to 69	62	16	2	15	0

70 to 79	69	12	4	10	2
Aged 80 and older	50	23	8	12	3
Unknown	1	0	0	2	0
Total	673	129	16	97	6

The estimated number of vaccinated persons, the number of reported adverse reactions, and the reporting frequency are shown by underlying disease and age group in Table 4. The number of vaccinated persons was calculated using the number of vaccinated persons reported by the contract medical institutions.

Table 4 Estimated number of vaccinated persons, number of reported adverse reactions and reporting frequency by underlying disorder and age group.

Reporting period		Vaccination from October 2010 to March 2011	Adverse reactions reported by medical institutions		Adverse reactions reported by the MAHs
			Number of reported adverse reactions (reporting frequency)		
Estimated number of vaccinated persons		Unit: 10,000 vaccinations		Number of serious adverse reactions (reporting frequency)	
Persons with underlying diseases	Under age of 15	45.0	59 0.01%	15 (1 fatal case) 0.003%	13 0.003%
	15 to 64	152.7	62 0.004%	23 (1 fatal case) 0.002%	15 (1 fatal case) 0.001%
	Aged 65 and older	434.2	82 0.002%	41 (14 fatal cases) 0.0009%	19 (5 fatal cases) 0.0004%
	Total	631.9	203 0.003%	79 (16 fatal cases) 0.001%	47 (6 fatal cases) 0.0007%
Pregnant women		23.0	3 0.001%	3 0.001%	0 0%
Under age of 15		1272.6	169 0.001%	20 0.0002%	21 0.0002%
15 to 64		1603.6	227 0.001%	26 0.0002%	17 0.0001%
Aged 65 and older		986.6	73 0.0007%	4 0.00004%	10 0.0001%
Unknown			1	0	2
Total		4517.7	673 0.001%	129 (16 fatal cases) 0.0003%	97 (6 fatal cases) 0.0002%

[unit: case]

(3) Specific topics of reported adverse reactions

A total of 84 cases of adverse reactions Note 1) were identified as possible Guillain-Barre syndrome or acute disseminated encephalomyelitis. Among the 84 cases, according to the expert assessment, causality to the vaccines in 10 cases of Guillain-Barre syndrome and 7 cases of acute disseminated encephalomyelitis could not be denied.

A total of 46 cases of adverse reactions were reported as possible anaphylaxis Note 2). Sixteen cases (11 serious cases) met Level 3 or higher of the Brighton Criteria.[1)] The reporting frequency of

adverse reactions of Brighton Criteria Level 3 or higher were 0.1/100000 vaccinations.

Nine cases of adverse reactions were reported as possible interstitial pneumonia.

Note 1) Including cases reported using the adverse reaction terms such as numbness, feeling of weakness, neuropathy, muscular weakness and difficulty swallowing

Note 2) Including cases reported using the adverse reaction terms of anaphylaxis, anaphylactic reaction, anaphylactic shock and anaphylactoid reaction

Table 5 presents a comparison of adverse reactions by system organ class between the 2009 influenza (H1N1) vaccine and the 2010 trivalent influenza vaccine. Adverse reactions assessed by the reporting physician as serious were tabulated as adverse reactions reported by the medical institutions.

Table 5 Comparison of adverse reactions to the 2009 influenza (H1N1) vaccine and the trivalent influenza vaccine

	2009 season	2010 season	
	2009 influenza (H1N1) vaccine	Trivalent influenza vaccine (H1N1 and seasonal bivalent)	
System Organ Class of adverse reaction*	Adverse reactions reported by medical institutions	Adverse reactions reported by medical institutions	Adverse reactions reported by MAHs
Blood and lymphatic system disorders	4	2	8
Cardiac disorders	40	3	3
Ear and labyrinth disorders	6	0	0
Eye disorders	6	1	3
Gastrointestinal disorders	31	5	2
General disorders and administration site conditions	132	48	31
Hepatobiliary disorders	17	5	6
Immune system disorders	59	21	5
Infections and infestations	22	11	6
Investigations	12	4	2
Metabolism and nutrition disorders	4	1	4
Musculoskeletal and connective tissue disorders	14	6	5
Nervous system disorders	123	51	36
Psychiatric disorders	2	1	1
Renal and urinary disorders	4	2	5
Respiratory, thoracic and mediastinal disorders	68	11	13
Skin and subcutaneous tissue disorders	32	16	24
Endocrine disorders	1	0	0
Pregnancy, puerperium and perinatal conditions	2	2	0
Vascular disorders	13	3	6
Total	592	193	160

* Adverse reaction terms coded in accordance with the MedDRA/J Ver. 14.0

A total of 22 fatal cases were reported following vaccination (Table 1). Although the data are limited, experts concluded that none of the deaths were directly or clearly associated with the vaccination.

3. Discussion about safety measures

Adverse reactions to the influenza HA vaccines (the influenza vaccines including the seasonal influenza vaccines for the 2008 and 2009 seasons and the trivalent vaccine for the 2010 season including the 2009 influenza (H1N1)) reported to the PMDA from April 1, 2008 to March 31, 2011were identified and reviewed to determine whether the Precautions section should be revised.

Based on the accumulated adverse reaction reports and the causality assessment, alerts against oculomucocutaneous syndrome, vasculitis, decreased appetite and meningitis were needed to be considered.

As shown in Table 6, several cases of oculomucocutaneous syndrome, vasculitis, and decreased appetite have been observed in which causality could not be ruled out. Alerts against these adverse reactions have already been included in the package inserts used in other countries overseas. Revision of the Precautions section was therefore considered appropriate. MHLW thus issued notification on August 9, 2011 and required the MAHs to revise the Precautions section of the package insert.

Table 6 Cases of adverse reactions over the last 3 years for which causality could not be ruled out

	Influenza HA vaccine (April 1, 2008 to March 31, 2011)
Oculomucocutaneous syndrome	1 case
Vasculitis	6 cases
Decreased appetite	1 case

According to an expert review, although there are some cases of meningitis for which causality to the influenza vaccination could not be ruled out, meningitis is unlikely to be related to the vaccination based on the temporal relationship between the vaccination and the onset of meningitis. The current package insert includes alerts against encephalitis/encephalopathy and myelitis. Healthcare professionals are considered to have already been alerted about the development of meningitis-like symptoms. Therefore, continuous attention will be paid to accumulated case reports without addition to the package insert for the time being.

4. Safety measures hereafter

The 2009 influenza H1N1 vaccination was switched to the seasonal influenza vaccination from April 1, 2011. Routine vaccinations are recommended for people aged 65 and older in accordance with the Preventive Vaccination Law, and younger people can voluntarily receive vaccinations. Adverse reactions to the vaccination in the 2011 season are to be directly reported from medical institutions to the MHLW as in the last season.[2)]

Medical institutions participating in the Vaccination Program are requested to carefully monitor adverse reactions to the influenza vaccines and promptly report adverse reactions which meet the Adverse Reaction Reporting Criteria (partially revised on September 29, 2011)[3)] for routine vaccinations and Reporting Adverse Reactions Associated with the Influenza Vaccines (HSB Notification No. 0929-3 and PFSB notification No. 0929-8, by the Secretary-General of Health Service Bureau and Pharmaceutical and Food Safety Bureau, dated September 29, 2011)[4)] for voluntary vaccinations. While the adverse reaction reporting criteria for routine vaccinations and voluntary vaccinations are different, the reporting form and the contact fax number of the MHLW are the same.

MHLW will continue to collect safety information such as adverse reaction reports and review the necessary of further safety measures.

<References> (including provisionally translated titles)

1) Ministry of Health, Labour and Welfare: Materials distributed at the 2010 Subcommittee on Drug Safety of Committee on Drug Safety (the fourth meeting) and the Influenza A (H1N1) Vaccine Adverse Reaction Review Committee (the first meeting) (the first joint meeting) (Reference 1-6; Classification and Assessment of Anaphylaxis)
http://www.mhlw.go.jp/stf/shingi/2r9852000000n6tv-att/2r9852000000n7l3.pdf (only available in Japanese language)
2) Ministry of Health, Labour and Welfare: Materials distributed at the 2011 Subcommittee on Drug Safety of Committee on Drug Safety (the fifth meeting) and the Vaccine Adverse Reaction Review Committee for Carcinoma of the Uterine Cervix (the second meeting) (the joint meeting) (Reference 2; The influenza vaccine adverse reaction reporting system in the 2011 season)
http://www.mhlw.go.jp/stf/shingi/2r9852000001ohxu-att/2r9852000001oi4k.pdf (only available in Japanese language)
3) Operating Procedure for Influenza Vaccination
http://www.mhlw.go.jp/bunya/kenkou/teiki-yobou/08.html (only available in Japanese language)
4) Reporting Adverse Reactions to Influenza Vaccines (HSB Notification No. 0929-3 and PFSB notification No. 0929-8, by the Secretary-General of Health Service Bureau and Pharmaceutical and Food Safety Bureau, dated September 29, 2011)
http://www.info.pmda.go.jp/iyaku/file/nt230929-001.pdf (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 September 20, 2011, the contents of important revisions and case summaries that served as the basis for these revisions are provided in this section.

1 Voriconazole

Brand Name (name of company)	VFEND Tablets 50 mg, 200 mg, VFEND 200 mg for Intravenous Use (Pfizer Japan Inc.)
Therapeutic Category	Acting mainly on mold
Indications	The following severe or refractory fungal infections • Invasive bronchopulmonary aspergillosis, pulmonary aspergilloma, chronic necrotic pulmonary aspergillosis • Candidaemia, oesophageal candidiasis*, candida peritonitis, bronchial/pulmonary candidiasis • Cryptococcal meningitis, pulmonary cryptococcosis • Fusariosis • Scedosporisis *: Only tablets are indicated for oesophageal candidiasis

PRECAUTIONS (underlined parts are revised)

Adverse Reactions (clinically significant adverse reactions)

Interstitial pneumonia: Interstitial pneumonia may occur. If cough, dyspnoea, pyrexia or abnormal chest sound (crepitations), etc. are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be performed and administration of this drug should be discontinued, and also appropriate measures including administration of corticosteroids should be taken.

Reference Information

The number of reported adverse reactions (for which causality to the drug could not be ruled out) for the past 3 years (April 1, 2008 to August 10, 2011)

- Interstitial pneumonia: 5 cases (no fatal cases)

The number of patients using this drug per year estimated by MAHs: approximately 30,000 (September 2010 to August 2011)

Launched in Japan: June 2005

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 70s	Bronchopulmonary aspergillosis (atypical mycobacterial infection, bronchiectasis, compression fracture,	Injection 400 mg for 1 day ↓ Injection 280 mg for 9 days	**Interstitial pneumonia (drug-induced pneumonia)** Approximately 10 months before administration: The patient was diagnosed with nontuberculous mycobacteriosis (*Mycobacterium kansasii*), and treated with isoniazid + rifampicin + ethambutol hydrochloride for about 1 year. Day 1 of administration: Bloody sputum and cough symptoms occurred. The chest X-ray showed cavitary opacities with surrounding

		appendicitis)		infiltrative shadow in the right upper lung field. Aspergillus was identified in bronchial lavage fluid, the patient was diagnosed with chronic necrotic pulmonary aspergillosis. Oral administration of voriconazole and itraconazole was started. Approximately Year 1 and Month 9 of administration (day of discontinuation): General malaise (non-serious) was severe. At the request of the patient, treatment with voriconazole and itraconazole was discontinued and follow-up observation was performed. Approximately 8 months after discontinuation: The chest X-ray showed increased infiltrative shadow and fungus ball inside the cavity in the right upper lung field. *Aspergillus flavus* was identified in bronchial lavage fluid, and the patient was diagnosed with aggravation of chronic pulmonary aspergillosis. Approximately 9 months after discontinuation: The patient was admitted to the hospital. Day 3 of hospitalisation: Drip infusion of cefepime dihydrochloride hydrate 1 g/day was started for bacterial pneumonia (for 6 days). Day 9 of hospitalisation (day of readministration): Drip infusion of voriconazole 400 mg/day was resumed. Day 2 of readministration: The dose of voriconazole was changed to 280 mg/day. Day 8 of readministration (day of onset): Shortness of breath on exercise and hypoxaemia were noted. Administration of oxygen 2L was started. Day 10 of readministration (day of discontinuation): The CT scan showed non-segmental reticular ground-glass opacity in the left lower lobe. The chest X-ray showed reticular ground-glass opacities in the left middle to lower lung fields. CRP was 5.79 mg/dL. Drug-induced pneumonia due to voriconazole was suspected based on the clinical course, and administration of voriconazole was discontinued from the evening of this day. 1 day after discontinuation of readministration: Oral administration of prednisolone 30 mg/day was started. The hypoxic state was gradually improved. 4 days after discontinuation of readministration: Bronchoscopy showed that bronchoalveolar lavage fluid was predominant lymphocyte. 8 days after discontinuation of readministration: Administration of oxygen was discontinued. CRP was 1.01 mg/dL. Shortness of breath on exercise also disappeared. 11 days after discontinuation of readministration: Drug-induced pneumonia remitted. Drug lymphocyte stimulation test (DLST) was negative for voriconazole in 3 days after discontinuation of readministration.
	Concomitant medications: dextromethorphan hydrobromide hydrate, tocopherol nicotinate, L-carbocisteine, loxoprofen sodium hydrate, antibiotics-resistant lactic acid bacteriae preparation, famotidine, erythromycin stearate, cherry bark extract/codeine phosphate hydrate, cefepime dihydrochloride hydrate			

Laboratory Examination

	Approx. 9 months after discontinuation	Day 7 of readministration	1 day after discontinuation of readministration	4 days after discontinuation of readministration	8 days after discontinuation of readministration	49 days after discontinuation of readministration
WBC (/mm^3)	9300	6100	5000	7600	8500	-
LDH (IU/L)	164	162	175	187	173	-
CRP (mg/dL)	2.48	5.60	5.79	2.29	1.01	-
KL-6 (U/mL)	-	347	325	-	-	307

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Male 60s	Bronchopulmonary aspergillosis (eosinophilic pneumonia)	Injection 400 mg for 14 days	**Interstitial pneumonia** Approximately 12 years before administration: The patient developed chronic necrotic pulmonary aspergillosis. Approximately 10 months before administration: Administration of itraconazole 200 mg/day was started. Approximately 7 months before administration: Concomitant eosinophilic pneumonia occurred. Approximately 6.5 months before administration: Administration of prednisolone 5 mg/day was started. Date unknown: The patient complained of slight fever and increased sputum. 2 days before administration: The chest X-ray showed cavitary lesion with fungus ball in the right upper lung field and infiltrative shadow in the left upper lung field. 1 day before administration: Administration of itraconazole was discontinued. Day 1 of administration: Administration of voriconazole was started for chronic necrotic pulmonary aspergillosis. Day 3 of administration (day of onset): The patient complained of pyrexia and general malaise. The chest X-ray showed ground-glass-like opacity (interstitial shadow) was noted in the right lower lobe in addition to the findings observed 2 days before administration. Recurrence of eosinophilic pneumonia was suspected, and administration of methylprednisolone sodium succinate 250 mg/day was started (for 3 days). Day 5 of administration: Administration of prednisolone 40 mg/day was started (for 4 days). Day 6 of administration: The chest X-ray showed improvement. Day 7 of administration: The patient complained of pyrexia and general strange feeling. Day 9 of administration: The chest X-ray showed interstitial shadow in the right lower lung. Aggravation of eosinophilic pneumonia was suspected, and administration of methylprednisolone sodium succinate 100 mg/day was started (for 3 days). Day 12 of administration: Administration of prednisolone 40 mg/day was started

				because the symptoms had improved. Day 14 of administration (day of discontinuation): Hyperthermia and skin eruption were noted. Interstitial pneumonia due to voriconazole was suspected, and administration of voriconazole was discontinued. 1 day after discontinuation: Administration of methylprednisolone sodium succinate 250 mg/day was started (for 3 days). 9 days after discontinuation: The chest X-ray showed improvement of ground-glass-like opacity in the right lower lung. 26 days after discontinuation: The patient recovered from interstitial pneumonia. Lung biopsy performed on Day 11 of administration showed lymphocytic infiltration, eosinophilic infiltration, and interstitial pneumonia.
	Concomitant medication: prednisolone			

Laboratory Examination

	13 days before administration	2 days before administration	Day 3 of administration (day of onset)	Day 11 of administration	1 day after discontinuation	18 days after discontinuation
WBC (/mm^3)	-	10500	8700	11600	13200	4700
LDH (IU/L)	-	129	152	173	196	140
CRP (mg/dL)	-	6.60	13.79	2.96	14.82	3.08
KL-6 (U/mL)	438	-	-	573	-	-

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 70s	Cryptococcal meningitis (none)	Injection 500 mg for 1 day ↓ Injection 320 mg for 17 days ↓ Tablet 300 mg for 4 days	**Interstitial pneumonia** 19 days before administration: The patient experienced pyrexia at 38°C and headache. 16 days before administration: Cerebrospinal fluid test was performed. The patient was admitted to the hospital, and administration of aciclovir and ceftriaxone sodium hydrate was started. 14 days before administration: Cerebrospinal fluid cell count increased, and cryptococcus was identified by culture. Administration of amphotericin B 150 mg/day was started. 10 days before administration: Administration of flucytosine 4000 mg/day was added. Day 1 of administration: Amphotericin B and flucytosine were switched to intravenous drip infusion of voriconazole 500 mg/day for treatment of meningitis cryptococcal. Day 2 of administration: The dose of voriconazole was reduced to 320 mg/day. Day 19 of administration (day of onset): In the morning, the administration route of voriconazole was switched from intravenous drip infusion to oral administration (300 mg/day). In the afternoon, pyrexia at 39°C and dry cough occurred. Pneumonia was suspected, sulbactam sodium/ampicillin

				sodium 6 g/day were administered. Day 20 of administration: The symptoms did not improve, and sulbactam sodium/ampicillin sodium were switched to meropenem hydrate 1 g/day. Day 22 of administration (day of discontinuation): The chest CT showed interstitial shadows in both lower lungs. The patient was diagnosed with interstitial pneumonia, and administration of voriconazole was discontinued. 2 days after discontinuation: Pyrexia resolved. 3 days after discontinuation: Administration of amphotericin B was started for treatment of cryptococcal meningitis. Administration of meropenem hydrate was discontinued. 13 days after discontinuation: The chest CT showed improvements of the shadows. The patient recovered from interstitial pneumonia. DLST was 143 cpm (negative) for voriconazole 10 days after discontinuation.
	Concomitant medications: aciclovir, ceftriaxone sodium hydrate			

Laboratory Examination

	4 days before administration	1 day before administration	Day 7 of administration	Day 11 of administration	Day 22 of administration (day of discontinuation)	13 days after discontinuation
WBC (/mm^3)	7800	6300	4300	4800	4400	6300
LDH (IU/L)	185	160	165	154	182	204
CRP (mg/dL)	4.99	3.52	1.61	1.05	22.40	2.61
KL-6 (U/mL)	-	-	-	-	299	-

5

Revision of Precautions (No. 230)

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 Notification dated September 20, 2011 (excluding those presented in 4. Important Safety Information of this Bulletin).

1

Diagnostic Agents-Miscellaneous

Gadoxetate Sodium

Brand Name

EOB・Primovist Inj. Syringe (Bayer Yakuhin, Ltd.)

Warnings

WARNINGS

It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with serious renal disorder. Caution should be exercised with patients with renal disorder or patients who may have decreased renal function.

Careful Administration

Patients with renal disorder or patients who may have decreased renal function.

Important Precautions

Serious adverse reactions, such as shock and anaphylactoid symptoms, may occur. Emergency measures should be prepared prior to administration of this drug. In addition, it has been reported that late-onset adverse reactions (pyrexia, rash, nausea, decreased blood pressure, dyspnoea, etc.) may occur 1 hour to several days after the start of administration of similar drugs. Patients should be carefully monitored after administration. Appropriate measures should be taken, such as instructing patients to contact their physician immediately if the above symptoms occur.

If this drug is administered to patients with renal disorder or patients who may have decreased renal function, this drug should be carefully administered after sufficient evaluation of the patient's renal function.

It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with end-stage renal disorder under long-term dialysis and patients with chronic renal disorder or acute renal failure whose eGFR (estimated glomerular filtration rate) is less than 30 mL/min/1.73 m^2. In such cases, administration of this drug should be avoided, and other alternative examination methods are encouraged.

Clinically significant adverse reactions (similar drug)

Nephrogenic Systemic Fibrosis (NSF): It has been reported that nephrogenic systemic fibrosis developed after using similar drugs in patients with serious renal disorder. Patients should be carefully monitored after administration, and caution should be exercised for the occurrence of abnormalities including itching, swelling, sclerosis of the skin, joint stiffness, and muscular weakness.

2

Diagnostic Agents-Miscellaneous

Gadodiamide Hydrate

Brand Name

OMNISCAN INTRAVENOUS INJECTION 32%, OMNISCAN INTRAVENOUS INJECTION 32% SYRINGE 5 mL, 10 mL, 15 mL, 20 mL

(Daiichi Sankyo Company, Limited)

Warnings

WARNINGS

It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with serious renal disorder. Caution should be exercised with patients with renal disorder or patients who may have decreased renal function.

Contraindications

Patients with serious renal disorder (Nephrogenic systemic fibrosis may occur. The main route of excretion of this drug is the kidney, and therefore, symptoms such as acute renal failure may be aggravated due to delayed excretion in patients with decreased renal function.)

Careful Administration

Patients with renal disorder or patients who may have decreased renal function.

Important Precautions

Serious adverse reactions such as shock and anaphylactoid symptoms may occur. Emergency measures should be prepared prior to administration of this drug. In addition, late-onset adverse reactions (pyrexia, rash, nausea, decreased blood pressure, dyspnoea, etc.) may occur 1 hour to several days after the start of administration of this drug. Patients should be carefully monitored after administration. Appropriate measures should be taken, such as instructing patients to contact their physician immediately if the above symptoms occur.

If this drug is administered to patients with renal disorder or patients who may have decreased renal function, this drug should be carefully administered after sufficient evaluation of the patient's renal function.

It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with end-stage renal disorder under long-term dialysis and patients with chronic renal disorder or acute renal failure whose eGFR (estimated glomerular filtration rate) is less than 30 mL/min/1.73 m^2. In such cases, administration of this drug should be avoided.

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3 **Diagnostic Agents-Miscellaneous**

Gadoteridol

Brand Name

ProHance for Intravenous Injection, 5 mL, 10 mL, 15 mL, 20 mL, ProHance for Intravenous Injection Syringe 13 mL, 17 mL (Bracco-Eisai Co., Ltd.)

Warnings

WARNINGS

It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with serious renal disorder. Caution should be exercised with patients with renal disorder or patients who may have decreased renal function.

Careful Administration

Patients with renal disorder or patients who may have decreased renal function.

Important Precautions

Serious adverse reactions such as shock and anaphylactoid symptoms may occur. Emergency measures against shock and anaphylactoid symptoms should be prepared prior to administration of this drug. In addition, it has been reported that late-onset adverse reactions (pyrexia, rash, nausea, decreased blood pressure, dyspnoea, etc.) may occur 1 hour to several days after the start of administration of similar drugs. Patients should be carefully monitored after administration. Appropriate measures should be taken, such as instructing patients to contact their physician immediately if the above symptoms occur.

If this drug is administered to patients with renal disorder or patients who may have decreased renal function, this drug should be carefully administered after sufficient

evaluation of the patient's renal function.
It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with end-stage renal disorder under long-term dialysis and patients with chronic renal disorder or acute renal failure whose eGFR (estimated glomerular filtration rate) is less than 30 mL/min/1.73 m^2. In such cases, administration of this drug should be avoided, and other alternative examination method are recommended.

Adverse Reactions (clinically significant adverse reactions)

Nephrogenic Systemic Fibrosis (NSF): It has been reported overseas that nephrogenic systemic fibrosis developed after using this drugs in patients with serious renal disorder. Patients should be carefully monitored after administration, and caution should be exercised for the occurrence of abnormalities including itching, swelling, and sclerosis of skin, joint stiffness, and muscular weakness.

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4 Diagnostic Agents-Miscellaneous

Meglumine Gadoterate

Brand Name

Magnescope intravenous injection 38% Syringe 10 mL, 15 mL, 20 mL, MAGNESCOPE Syringe (Guerbet Japan K.K.)

Warnings

WARNINGS

It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with serious renal disorder. Caution should be exercised with the patients with renal disorder or patients who may have decreased renal function.

Careful Administration

Patients with renal disorder or patients who may have decreased renal function.

Important Precautions

Shock and anaphylactoid symptoms may occur. Emergency measures should be prepared prior to administration of this drug. In addition, it has been reported that late-onset adverse reactions (pyrexia, rash, nausea, decreased blood pressure, dyspnoea, etc.) may occur 1 hour to several days after the start of administration of similar drugs. Patients should be carefully monitored after administration. Appropriate measures should be taken, such as instructing patients to contact their physician immediately if the above symptoms occur.
If this drug is administered to patients with renal disorder or patients who may have decreased renal function, this drug should be carefully administered after sufficient evaluation of the patient's renal function.
It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with end-stage renal disorder under long-term dialysis and patients with chronic renal disorder or acute renal failure whose eGFR (estimated glomerular filtration rate) is less than 30 mL/min/1.73 m^2. In such cases, administration of this drug should be avoided, and other alternative examination method are recommended.

Adverse Reactions (clinically significant adverse reactions)

Nephrogenic Systemic Fibrosis (NSF): It has been reported overseas that nephrogenic systemic fibrosis developed after using this drugs in patients with serious renal disorder. After administration, patients should be carefully monitored, and caution should be exercised for the occurrence of abnormalities including itching, swelling, and sclerosis of skin, joint stiffness, and muscular weakness.

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5 Diagnostic Agents-Miscellaneous

Gadopentetate Dimeglumine

Brand Name

Magnevist iv inj., Magnevist iv inj. Syringe (Bayer Yakuhin, Ltd.)

Warnings	**WARNINGS** It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with serious renal disorder. Caution should be exercised with the patients with renal disorder or patients who may have decreased renal function.
Contraindications	Patients with serious renal disorder (Nephrogenic systemic fibrosis may occur. The main organ that excretes this drug is the kidney, and therefore, symptoms such as acute renal failure may be aggravated due to delayed excretion in patients with decreased renal function.)
Careful Administration	Patients with renal disorder or patients who may have decreased renal function.
Important Precautions	Emergency measures against shock and anaphylactoid symptoms should be prepared prior to administration of this drug. In addition, late-onset adverse reactions (pyrexia, rash, nausea, decreased blood pressure, dyspnoea, etc.) may occur 1 hour to several days after the start of administration of this drug. Patients should be carefully monitored after administration. Appropriate measures should be taken, such as instructing patients to contact their physician immediately if the above symptoms occur. If this drug is administered to patients with renal disorder or patients who may have decreased renal function, this drug should be carefully administered after sufficient evaluation of the patient's renal function. It has been reported that the risk of development of nephrogenic systemic fibrosis due to gadolinium contrast media is increased in patients with end-stage renal disorder under long-term dialysis and patients with chronic renal disorder or acute renal failure whose eGFR (estimated glomerular filtration rate) is less than 30 mL/min/1.73 m^2. In such cases, administration of this drug should be avoided.

6 **Antiepileptics**

Carbamazepine

Brand Name	Tegretol Tablet 100 mg, 200 mg, Tegretol Fine granule 50% (Novartis Pharma K.K.)
Other Precautions	A retrospective genome-wide association analysis in Japanese reported that HLA-A*3101 carriers accounted for 58% (45/77) of patients who developed serious drug eruption associated with this drug such as oculomucocutaneous syndrome, toxic epidermal necrolysis, and hypersensitivity syndrome, while HLA-A*3101 carriers accounted for 13% (54/420) of patients who did not develop severe drug eruption. Retrospective studies in patients of Han Chinese descent have found that almost all of the patients with oculomucocutaneous syndrome or toxic epidermal necrolysis associated with this drug were carriers of HLA-B*1502. On the other hand, apparent association between severe drug eruption associated with this drug and carriers of HLA-B*1502 was not suggested in the research conducted in Japanese. Meanwhile, it was reported that the frequency of HLA-B*1502 allele is 0.019 - 0.124 in Han Chinese and 0.001 in Japanese.
Reference Information	Ozeki, T., et al. : Hum. Mol. Genet. 2011 ; 20(5): 1034-1041 Middleton, D., et al. : Tissue Antigens 2003 ; 61 (5): 403-407

7

Anticoagulants

Dabigatran Etexilate Methanesulfonate

Brand Name	Prazaxa Capsules 75 mg, 110 mg (Nippon Boehringer Ingelheim Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Interstitial pneumonia**: Interstitial pneumonia may occur. Patients should be carefully monitored. If cough, dyspnoea, pyrexia or abnormal chest sound, etc. are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be performed immediately. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures including administration of corticosteroids should be taken.

8

Anticoagulants

Fondaparinux Sodium

Brand Name	Arixtra Injection 1.5 mg, 2.5 mg, 5 mg, 7.5 mg (GlaxoSmithKline K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Hepatic dysfunction, jaundice**: Hepatic dysfunction with elevations of AST (GOT), ALT (GPT) or jaundice may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

9

Blood and body fluid agents-Miscellaneous

Clopidogrel Sulfate

Brand Name	Plavix Tablets 25 mg, 75 mg (Sanofi-aventis K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Gastric/duodenal ulcer**: Haemorrhagic gastric/duodenal ulcer may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

10

Miscellaneous metabolism agents-Miscellaneous

Sodium Hyaluronate Crosslinked Polymer/Sodium Hyaluronate Crosslinked Polymer Crosslinked with Vinylsulfone

Brand Name	SYNVISC Intraarticular Injection 2 mL (Genzyme Japan K.K.)
Adverse Reactions (clinically significant adverse reactions)	**Arthritis**: Arthritis associated with pyrexia, pain, or oedema may occur. Appropriate measures should be taken. Patients should be thoroughly informed of this risk and be instructed to contact their physician if these symptoms occur.

11

Antimetabolites

Capecitabine

Brand Name	XELODA Tablet 300 (Chugai Pharmaceutical Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Oculomucocutaneous syndrome (Stevens-Johnson syndrome)**: Oculomucocutaneous syndrome may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

12

Synthetic antibacterials

Garenoxacin Mesilate Hydrate

Brand Name	Geninax Tablets 200 mg (Toyama Chemical Co., Ltd.)
Adverse Reactions (clinically significant adverse reactions)	**Fulminant hepatitis, hepatic dysfunction**: Fulminant hepatitis, or hepatic dysfunction with significant elevations of AST (GOT) and ALT (GPT) may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken. **Agranulocytosis, decreased platelets**: Agranulocytosis or decreased platelets may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

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 Marketing Authorization Holder is responsible for collecting the adverse drug reactions (ADRs) from all of the medical institutions where the drugs are used and for taking safety measures. The aim of the EPPV is to promote the rational proper use of the drug in medical treatments, and to promptly take actions for prevention of the serious adverse drug reactions. EPPV is specified as a condition of approval.

(As of October 1, 2011)

Nonproprietary name Brand name	Name of the marketing authorization holder	Date of EPPV initiate
Eldecalcitol EDIROL Capsule 0.5 μg, 0.75 μg	Chugai Pharmaceutical Co., Ltd.	April 11, 2011
Freeze-dried, Cell Culture-Derived Japanese Encephalitis Vaccine (Inactivated) ENCEVAC Subcutaneous Injection	The Chemo-Sero-Therapeutic Research Institute	April 11, 2011
Romiplostim (Genetical Recombination) Romiplate for s.c. injection 250 μg	Kyowa Hakko Kirin Co., Ltd.	April 13, 2011
Anti-human Thymocyte Immunoglobulin, Rabbit Thymoglobuline for Intravenous Infusion 25 mg*1	Genzyme Japan K.K.	April 22, 2011
Doripenem Hydrate FINIBAX for Drip Infusion 0.25 g, FINIBAX Kit for Drip Infusion 0.25 g*2	Shionogi & Co., Ltd.	April 22, 2011
Levobupivacaine Hydrochloride POPSCAINE 0.25% inj. 25 mg/10mL, POPSCAINE 0.25% inj. syringe 25 mg/10 mL*3	Maruishi Pharmaceutical Co., Ltd.	April 22, 2011
Repaglinide SUREPOST Tablets 0.25 mg, 0.5 mg	Dainippon Sumitomo Pharma Co., Ltd.	May 16, 2011
Febuxostat Feburic Tablet 10 mg, 20 mg, 40 mg	Teijin Pharma Limited	May 17, 2011
Levonorgestrel NORLEVO 0.75 mg Tablet	Sosei Co. Ltd.	May 24, 2011
Pioglitazone Hydrochloride/Glimepiride SONIAS Combination Tablets LD & HD	Takeda Pharmaceutical Company Limited	June 6, 2011
Memantine Hydrochloride MEMARY TABLETS 5 mg, 10 mg, 20 mg	Daiichi Sankyo Company, Limited	June 8, 2011
Adalimumab (Genetical Recombination) HUMIRA for s.c. injection syringe 40 mg/0.8 mL, HUMIRA for s.c. injection syringe 20 mg/0.4 mL*4	Abbott Japan Co., Ltd.	July 1, 2011
Erlotinib Hydrochloride TARCEVA Tablets 25 mg, 100 mg*5	Chugai Pharmaceutical Co., Ltd.	July 1, 2011

Gabapentin GABAPEN Tablets 200 mg, 300 mg, 400 mg*[6]	Pfizer Japan Inc.	July 1, 2011
Peginterferon Alfa-2a (Genetical Recombination)	Chugai Pharmaceutical Co., Ltd.	July 1, 2011*[7]
PEGASYS s.c. 90 μg, 180 μg		September 26, 2011*[8]
Lamotrigine Lamictal Tablets 25 mg, 100 mg*[9]	GlaxoSmithKline K.K.	July 1, 2011
Ribavirin COPEGUS Tablet 200 mg*[10]	Chugai Pharmaceutical Co., Ltd.	July 1, 2011
Edoxaban Tosilate Hydrate LIXIANA TABLETS 15 mg, 30 mg	Daiichi Sankyo Company, Limited	July 19, 2011
Eribulin Mesilate Halaven injection 1 mg	Eisai Co., Ltd.	July 19, 2011
Tramadol Hydrochloride/Acetaminophen TRAMCET Combination Tablets	Janssen Pharmaceutical K.K.	July 19, 2011
Rivastigmine EXELON PATCH 4.5 mg, 9 mg, 13.5 mg, 18 mg	Novartis Pharma K.K.	July 19, 2011
Rivastigmine RIVASTACH Patch 4.5 mg, 9 mg, 13.5 mg, 18 mg	Ono Pharmaceutical Co., Ltd.	July 19, 2011
Epoetin Beta Pegol (Genetical Recombination) MIRCERA Injection Syringe 25 μg, 50 μg, 75 μg, 100 μg, 150 μg, 200 μg, 250 μg	Chugai Pharmaceutical Co., Ltd.	July 20, 2011
Pramipexole Hydrochloride Hydrate Mirapex-LA Tablets 0.375 mg, 1.5 mg	Nippon Boehringer Ingelheim Co., Ltd.	July 20, 2011
Mitiglinide Calcium Hydrate/Voglibose GLUBES Combination Tab.	Kissei Pharmaceutical Co., Ltd.	July 22, 2011
Desflurane Suprane Inhalational Anesthetic Solution	Baxter Limited	July 29, 2011
Buprenorphine NORSPAN TAPE 5 mg, 10 mg, 20 mg	Mundipharma K.K.	August 4, 2011
Escitalopram Oxalate LEXAPRO Tab. 10mg	Mochida Pharmaceutical Co., Ltd.	August 22, 2011
Recombinant Adsorbed Quadrivalent Human Papillomavirus Virus-Like Particle Vaccine (Yeast Origin) GARDASIL Aqueous Suspension for Intramuscular Injection, GARDASIL Aqueous Suspension for Intramuscular Injection Syringe	MSD K.K.	August 26, 2011
Pancrelipase LipaCreon Granules 300mg Sachet, LipaCreon Capsules 150mg	Abbott Japan Co., Ltd.	August 30, 2011
Vorinostat ZOLINZA Capsules 100 mg	MSD K.K.	September 14, 2011
Esomeprazole Magnesium Hydrate Nexium Capsules 10 mg, 20 mg	AstraZeneca K.K.	September 15, 2011
Landiolol Hydrochloride COREBETA for Intravenous 12.5 mg	Ono Pharmaceutical Co., Ltd.	September 15, 2011
Linagliptin Trazenta Tablets 5 mg	Nippon Boehringer Ingelheim Co., Ltd.	September 15, 2011
Golimumab (Genetical Recombination) Simponi Subcutaneous Injection Syringe 50 mg	Janssen Pharmaceutical K.K.	September 16, 2011

Minodronic Acid Hydrate Bonoteo Tablets 50 mg	Astellas Pharma Inc.	September 16, 2011
Minodronic Acid Hydrate RECALBON Tablets 50 mg	Ono Pharmaceutical Co., Ltd.	September 16, 2011
Mirabegron Betanis Tablets 25 mg, 50 mg	Astellas Pharma Inc.	September 16, 2011
Alogliptin Benzoate / Pioglitazone Hydrochloride LIOVEL Combination Tablets LD & HD	Takeda Pharmaceutical Company Limited	September 20, 2011
Indacaterol Maleate onbrez inhalation capsules 150 μg	Novartis Pharma K.K.	September 20, 2011
Daptomycin CUBICIN IV 350 mg	MSD K.K.	September 22, 2011
Itraconazole ITRIZOLE Oral Solution 1%*[11]	Janssen Pharmaceutical K.K.	September 26, 2011
Bevacizumab (Genetical Recombination) AVASTIN 100 mg/4 mL Intravenous Infusion, AVASTIN 400 mg/16 mL Intravenous Infusion*[12]	Chugai Pharmaceutical Co., Ltd.	September 26, 2011

*1 An additional indication for “treatment of acute rejection after renal transplantation”

*2 An additional dosage and administration for “maximum daily dose, 3 g”

*3 An additional indication for “conduction anesthesia”

*4 An additional indication for “treatment of patients with active polyarticular juvenile idiopathic arthritis”

*5 An additional indication for “treatment of patients with non-resectable pancreatic carcinoma”

*6 An additional administration for “pediatrics”

*7 An additional indication for “improvement of viraemia in compensated cirrhosis C in combination therapy with ribavirin”

*8 An additional indication for “improvement of viraemia in chronic active hepatitis B”

*9 An additional indication for “suppression of recurrent/relapsed mood episodes in patients with bipolar disorder”

*10 An additional indication for “improvement of viraemia in compensated cirrhosis C in combination therapy with peginterferon alfa-2a (genetical recombination)”

*11 Additional indications for “treatment of patients with fungal infection caused by *Aspergillus*, *Cryptococcus*, *Blastomyces*, or *Histoplasma* (fungaemia, respiratory mycosis, gastrointestinal mycosis, urinary tract mycosis, fungal meningitis, blastomycosis, histoplasmosis)”, “treatment of patients with febrile neutropenia of suspected fungal infection”, and “prophylaxis of deep mycosis in patients with haematological malignancy possibly associated with neutropenia or patients who underwent hematopoietic stem cell transplantation”

*12 An additional indication for “treatment of patients with inoperable or recurrent breast cancer”