Pharmaceuticals and Medical Devices Safety Information

No. 273 October 2010

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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).

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Pharmaceuticals and Medical Devices Safety Information
No. 273 October 2010

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

[Outline of Information]

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.

1

The Relief System for Sufferers from Adverse Drug Reactions and Diseases Infected from Biological Products

1. Introduction

The Relief System for Sufferers from Adverse Drug Reactions was established in 1980 to bring prompt relief to people who suffer from adverse health effects such as disorders or disabilities caused by adverse reactions of pharmaceuticals (including over-the-counter drugs), despite using them properly. This is a public service funded by contributions from marketing authorization holders of pharmaceutical and biological products as a way to fulfill some of their social responsibilities. As of August 31, 2010, approximately 8,000 people (the actual number) have been granted relief benefits.

In 2004, the Relief System for Sufferers from Diseases Infected from Biological Products, which is also a public service, was established to bring prompt relief to people who suffered from adverse health effects including disorders or disabilities caused by infections from biological products, despite using them properly.

For details of these services, please refer to the website of the PMDA at http://www.pmda.go.jp/kenkouhigai.html (only available in Japanese language).

Recently, the number of applications for the Relief System for Sufferers (Relief System for Sufferers from Adverse Drug Reactions and Diseases Infected from Biological Products, the same shall apply hereafter) has been increasing (1,052 claims were submitted to Relief System for Sufferers in the fiscal year [FY] 2009). In response to criticisms that this relief system is still not well known to the public, however, the procedures for claiming relief benefits (information to be provided to sufferers from adverse health effects) and examples of cases approved for relief benefits are presented here to encourage people who have suffered adverse health effects to further use these services.

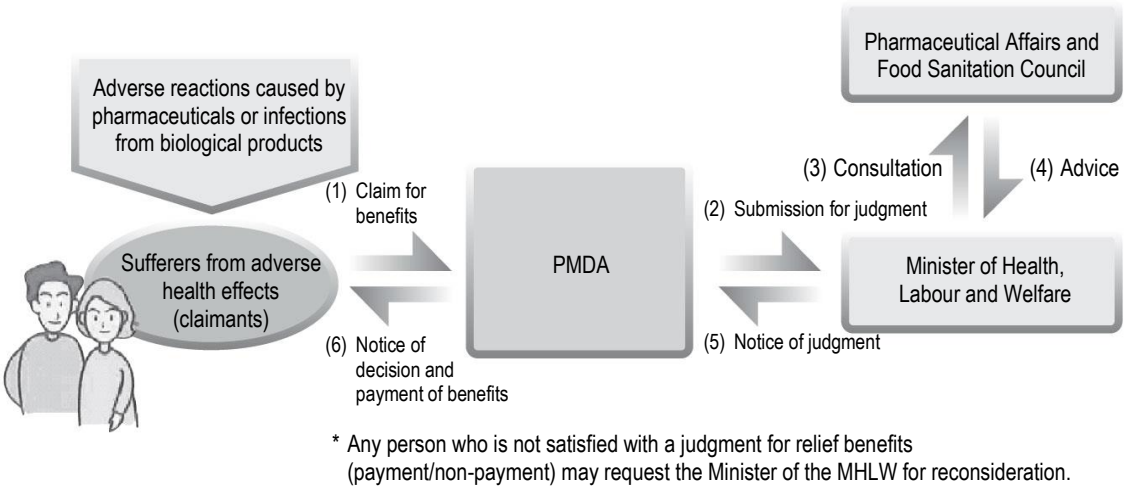
2. Procedures for claiming relief benefits (information to be provided to sufferers from adverse health effects)

When healthcare providers are consulted by their patients on disorders or disabilities which are suspected to have been caused by adverse health effects of pharmaceutical or biological products, they should provide information regarding this system and the following matters to the patients suffering from adverse health effects, or to the bereaved families of the sufferers.

(1) How to claim for relief benefits

Claims for relief benefits should be submitted by the patients suffering from adverse health effects caused by pharmaceutical or biological products, or by their bereaved family (hereinafter "claimants") directly to the PMDA.

Flowchart of the relief system



(2) Types of benefits and deadlines for claiming

There are 7 benefit types: Medical Expenses, Medical Allowances, Disability Pension, Pension for Raising Handicapped Children, Bereaved Family Pension, Lump-sum Benefits for Bereaved Families, and Funeral Expenses (For details of each benefit and deadlines for claiming, refer to **Document 1** on pages 8 to 10).

(3) Documents required for claiming

○ Physician's certificate, ○ Proof of prescription, ○ Proof of medical examination, etc.

To receive relief benefits, it is necessary to establish the causality between a disorder and/or disability and pharmaceuticals, etc.

When claiming for a relief benefit, the following documents are required; a) a medical certificate written by the physician who treated the adverse health effects caused by adverse reactions or infections, b) a proof of prescription, or c) a proof of purchase if the over-the-counter drug was purchased from a pharmacy or drugstore. Claimants submit to the PMDA the above documents written by their physicians and/or pharmacists, together with the claims filled out by the claimants.

All required forms, including claim forms and medical certificate forms, are available from the PMDA and can be sent free of charge upon the request of claimants by the PMDA. The necessary forms can also be downloaded from the PMDA's websites (http://www.pmda.go.jp/kenkouhigai/fukusayo_dl/ for the Relief System for Sufferers from Adverse Drug Reactions and http://www.pmda.go.jp/kenkouhigai/kansen_dl/ for the Relief System for Sufferers from Diseases Infected from Biological Products).

(4) Contact office for the Relief System for Sufferers

The documents required to claim relief benefits include a written request for relief according to the relief benefit type, a physician's certificate (with diagnosis), a proof of medical examination, and a proof of prescription. When claiming the relief benefits, please contact the PMDA Relief System Consultation Service by phone or E-mail in advance.

Pharmaceuticals and Medical Devices Agency
(Relief System Consultation Service)
Telephone: 0120-149-931 (a toll-free number)
Operating hours: [Monday to Friday] 9:00-17:30 (excluding national holidays and New Year holidays)
E-mail: kyufu@pmda.go.jp
Website: http://www.pmda.go.jp/kenkouhigai.html (only available in Japanese language)

3. Example cases of relief benefit payments

(1) Cases approved for relief benefits

In this section, specific cases where relief benefits have been approved are presented. In addition, the details regarding payment/non-payment of adverse reaction relief benefits (including name of drug [brand name], name and description of the adverse reaction, description of the benefit, and reason for non-payment) are disclosed on the PMDA's website (http://www.pmda.go.jp/kenkouhigai/help/information.html, only available in Japanese language).

[Relating to Medical Expenses/Medical Allowances]

<Granulocytopenia>

Female in her 30s. Thiamazole was prescribed for treatment of Basedow's disease. Blood tests were performed approximately every 2 weeks during treatment. She developed pharynx pain approximately 3 months after the administration. She immediately consulted the doctor as instructed by the prescribed physician. Because granulocytopenia was detected by the laboratory test, Thiamazole treatment was discontinued. She was admitted to the hospital for further treatment for approximately 2 weeks.

<Oculomucocutaneous syndrome (Stevens-Johnson syndrome)>

Female in her 20s. Acetaminophen and cefcapene pivoxil hydrochloride hydrate were prescribed to the patient for treatment of pharyngitis. Around noon the following day, she developed fever, oral erosion and many red papulae on her trunk. After 4 days severe fever persisted, swelling of her face, lip and oral erosion, corneal and conjunctival disorders, vulval lesion, and oedematous erythema on the limbs-trunk were observed. She was admitted to the hospital and underwent steroid pulse therapy, etc. She remained hospitalized for 19 days.

[Relating to Disability Pension/Pension for Raising Children with disabilities]

<Toxic optic neuropathy>

Male in his 70s. Ethambutol hydrochloride, rifampicin, isoniazid, etc. were prescribed to the patient for treatment of pulmonary tuberculosis. After approximately 3 months of the use of the drugs, he noticed visual abnormalities and visited a medical institution. His visual acuity was measured to be 0.1 (20/200)* in each eye; thus, administration of ethambutol hydrochloride was discontinued. There has been no tendency for improvement since then, and at present acuity is 0.02 (20/1000)* in the right eye and 0.03 (20/667)* in the left eye.

＊Visual acuity written in decimal visual acuity (fractional visual acuity)

[Regarding Bereaved Family Pension/Lump-sum Benefits for Bereaved Families/ Funeral Expenses]

<Anaphylactoid shock>

Male in his 60s. Ceftriaxone sodium hydrate was administered by intravenous infusion for treatment of acute bronchitis. After approximately three and a half minutes of administration, he looked ill and developed vomiting, cough, and hyperaemia of bulbar conjunctiva. And thus the infusion was discontinued. Steroid administration, oxygen inhalation, and aspiration were performed. Then the pulse became weak, and he collapsed in a state of shock. Cardiac massage, oxygen inhalation, and endotracheal intubation were performed. He died despite of infusion of epinephrine and cardiopulmonary resuscitation.

(2) Examples of cases not applicable for relief benefits

As of August 31, 2010, approximately 8,000 people have been approved for relief benefits as of August 31, 2010, while it has been decided that approximately 1,400 people will not be paid relief benefits.

The following cases are not applicable under the Relief System for Sufferers:

a. Cases of adverse health effects resulting from standard vaccination practice (Relief System for

Injury to Health with Vaccination is applicable in such cases). However, cases of adverse health effects resulting from voluntary vaccinations are applicable under the Relief System for Sufferers.

b. Cases where it is clear who is responsible for adverse health effects, including in the case of product liability of the marketing authorization holders of the pharmaceutical or biological product.
c. Cases where it is necessary to use the pharmaceutical or biological product in an amount exceeding the approved dosage for the purpose of saving the patient's life, even if it was recognized beforehand that adverse health effects may occur.
d. Cases where the pharmaceutical or biological product was used improperly or for an improper purpose.
e. Cases of adverse health effects caused by pharmaceuticals that are not applicable to the relief benefits.
   Pharmaceuticals that are not applicable to relief benefits include:
   (1) Pharmaceuticals used in the treatment of cancer or other specific disorders designated by the Minister of Health, Labour and Welfare (i.e. anticancer drugs, immunosuppressants, etc.)
   (2) Pharmaceuticals that do not have the possibility to cause adverse reactions, including pharmaceuticals not used directly on human bodies or pharmaceuticals without pharmacological effects (i.e. insecticides, antimicrobial agents, in vitro diagnostics [IVDs], etc.)
f. Cases of mild adverse health effects (including a case where admission to a hospital or treatment equivalent to inpatient care is not required), or where the deadline of claiming the relief benefits has passed.

Reasons and details of non-applicable cases for the relief benefits in FY 2009 are described below (refer to **Document 2** on pages 10 to 11). As reasons for decision of non-payment, "No causality" accounted for 43%. The relief system is not applicable in cases where the causality between adverse health effects and the pharmaceuticals is not confirmed.

Secondly, "The cases that do not require admission nor meet the disability criteria" accounted for 21%. The relief benefits are not approved in cases where admission to a hospital or treatment equivalent to inpatient care is not required, even if causality between the pharmaceuticals and the disorders has been confirmed. The relief benefits are also not approved in cases where the disabilities caused by pharmaceuticals fail to meet the disability criteria defined under the system, even if causality between the disabilities and the pharmaceuticals has been confirmed.

The cases of "Improper purpose or improper use (Pharmaceuticals or biological products were not used for approved indications or in accordance with appropriate instructions)" accounted for 20%. Even if adverse health effects occurred or not, cases where pharmaceutical or biological products are used in noncompliance with the Precautions section in the package inserts may not be applicable under the Relief System for Sufferers.

4. Closing comments

Understanding and cooperation of physicians, pharmacists, and other healthcare professionals are essential to provide the relief benefits to sufferers from adverse health effects under the Relief System for Sufferers.

Adverse reactions can be an unpreventable consequence of pharmaceutical administration, even if pharmaceuticals are used according to instructions with all possible care. Therefore, the relief for sufferers from adverse health effects should be achieved by this system for prompt relief benefits, apart from civil responsibility. Some healthcare professionals are unwilling to provide diagnosis certificates and/or other documents required in claiming for relief benefits, as they misunderstand such documents as being an admittance of inappropriate medical practice that may have caused the adverse health effects. This system aims to provide prompt relief benefits to people suffering from adverse health effects caused by pharmaceuticals in all respects. The certificates and/or other proofs provided by healthcare professionals are the useful reference materials and play an important role in the

decision making process regarding these relief benefits.

As mentioned in Section 2, when adverse reactions occur, or when healthcare professionals are consulted by their patients about the adverse reactions, and it is suspected to be possibly applicable for these relief benefits, the healthcare professionals should provide information regarding these services to the patients. The PMDA hopes for your continued cooperation in preparing the documents required to claim these relief benefits.

Document 1. Details of benefits and claim deadline, etc. of the Relief System for Sufferers

In cases of disorder (requiring admission)

Medical expenses

Compensation will reflect actual costs of treatment for disorders caused by the adverse reactions of pharmaceuticals, etc. borne by the patient.

The coverage of Medical Expenses includes treatment for disorders requiring admission, which is caused by the adverse reactions of pharmaceuticals, etc. and situations which require an equivalent level of treatment. The disorders requiring admission are not limited to the cases where the patients were actually admitted to hospitals. Patients treated at their home for various reasons can also be applicable for Medical Expenses, if the disorders are considered as having an equivalent level of disorder to that requiring admission.

[Claim deadline] Within 2 years since the payment of costs applicable for Medical Expense Benefit (however, for the costs that were paid from May 1, 2008, the claim should be made within 5 years).

[Claimant] The person who received treatment for disorders caused by adverse reactions, etc.

Medical Allowances

Benefits are provided for costs other than medical costs (round-trip transportation expenses to a hospital, miscellaneous expenses accompanying admission, etc.) for treatment of disorders caused by adverse reactions to pharmaceuticals, etc. The coverage of Medical Allowances includes the treatments for disorders requiring admission, similar to the coverage of Medical Expenses, in principle.

Medical Allowances are paid on a monthly basis. The amount of payment as of April 1, 2010 is as follows:

〈In case with outpatient treatment only〉	
A case with 3 days and more of outpatient treatments a month	35,800 yen (monthly amount)
A case with less than 3 days of outpatient treatments a month	33,800 yen (monthly amount)
〈In case with admission only〉	
A case with 8 days and more of admission a month	35,800 yen (monthly amount)
A case with less than 8 days of admission a month	33,800 yen (monthly amount)
〈In case with both admission and outpatient treatments〉	35,800 yen (monthly amount)

[Claim deadline] Within 2 years since the first day of the next month of the month when the treatment may be covered by the Medical Allowance was made (however, for a treatment that was given from May 1, 2008, claims are due within 5 years).

[Claimant] The person who received treatment for disorders caused by adverse reactions, etc.

In cases of a certain degree of disability (causing at least significant activity limitation during daily life)

Disability Pension

Benefits are provided to compensate for living costs, etc. of patients aged 18 or older, who suffer from a certain degree of disabilities caused by adverse reactions of pharmaceuticals, etc.

The degree of disability is classified as Grade 1 or Grade 2. The outline of each grade is as follows:

(1) Grade 1: A degree of disability that prevents a person from performing activities during their daily life by themselves
(A level at which full assistance is needed during daily life)
(2) Grade 2: A degree of disability that significantly limits a person from performing activities during their daily life or that results in significant limitation of their performance during their daily life
(A level at which assistance is not always needed, but at which the person's performance during their daily life is significantly limited)

The amount of payment as of April 1, 2010 is as follows:
(1) Grade 1: Annual amount of 2,720,400 yen (monthly amount of 226,700 yen)
(2) Grade 2: Annual amount of 2,175,600 yen (monthly amount of 181,300 yen)

[Claim deadline] Deadline for the claim is not specified.
[Claimant] The person with disability caused by adverse reactions, etc. (aged 18 or older)

Pension for Raising Children with disabilities

Benefits are provided for those who are responsible for raising children under age of 18 who suffer from a certain degree of disability caused by adverse reactions of pharmaceuticals, etc.

A person who is responsible for raising a child with disability refers to a person who is socially accepted as raising such a child by comprehensively considering whether the person has the custody of the child, lives with the child, and supports the livelihood of the child. The degrees of disabilities are the same as those of Disability Pension.

The amount of payment as of April 1, 2010 is as follows:
(1) Grade 1: Annual amount of 850,800 yen (monthly amount of 70,900 yen)
(2) Grade 2: Annual amount of 680,400 yen (monthly amount of 56,700 yen)

[Claim deadline] Deadline for the claim not specified.
[Claimant] The person who is responsible for raising a child under age of 18 with disability caused by adverse reactions, etc.

In cases of death

Bereaved Family Pension

Benefits are provided for bereaved families to rebuild their lives following the deaths of their main providers from adverse reactions of pharmaceuticals, etc.

The maximum period for payment of Bereaved Family Pension is 10 years. The amount of payment as of April 1, 2010 is 2,378,400 yen per year (198,200 yen per month).

[Claim deadline] Within 5 years after the death.
However, in such a case where Medical Expenses, Medical Allowances, Disability Pension, or Pension for Raising Children with disabilities has decided to be approved, the claim should be made within 2 years after the death.
[Claimant] The person in the highest order of priority in the bereaved family who lived in the same household with the person (main provider) who died from adverse reactions, etc.
The order of priority is (1) spouse, (2) child, (3) father or mother, (4) grandchild, (5) grandfather or grandmother, and (6) brother or sister (a spouse includes a person in circumstances similar to a registered marriage).

Lump-sum Allowances for Bereaved Family

Benefits are provided for bereaved families for condolence and sympathy following the death from adverse reactions of pharmaceuticals, etc. of their family member who is not the main provider.

For Lump-sum Benefits for Bereaved Family, the equivalence of amount for 36 months of

Bereaved Family Pension is paid. The amount of payment as of April 1, 2010, is 7,135,200 yen.

[Claim deadline] Same as for Bereaved Family Pension.
[Claimant] The person in the highest order of priority in the bereaved family who lived in the same household with the person (other than main provider) who died from adverse reactions, etc. (For the order of priority, refer to the section of Bereaved Family Pension).

Funeral Expenses

Benefits are provided to a person who holds a funeral for the costs of holding the funeral for the person who died from adverse reactions of pharmaceuticals, etc.

The amount of payment as of April 1, 2010, is 201,000 yen.

[Claim deadline] Same as for Bereaved Family Pension
[Claimant] The person who holds the funeral of the person died from adverse reactions, etc.

Document 2. Reasons and details for non-payment for the relief benefits, etc.

This section describes the reasons for (decision of) non-payment for the relief benefits under the Relief System for Adverse Drug Reactions.

The proportion of non-payment decision accounted for approximately 13% of all claims in FY 2009. (The total number of payment and non-payment was 990 claims. Out of them, non-payment decisions were made against 127 claims.)

The reasons for non-payment (FY 2009) are "No causality" (43%), "The cases that do not require admission nor meet the disability criteria" (21%), "Improper purpose or improper use" (20%), "Impossible to judge" (13%), "Pharmaceuticals inapplicable to the relief benefits" (2%), and "Others" (1%).

No causality

"No causality" refers to cases in which the disorders or disabilities are not likely to be caused by adverse reactions of pharmaceuticals.

The cases that do not require admission nor meet the disability criteria

"The cases that do not require admission nor meet the disability criteria" refer to cases in which although the causality between pharmaceuticals and the disorder is confirmed, admission to a hospital or treatment equivalent to the inpatient care is not required, or does not meet the criteria of "Disability that prevents a person from performing daily life activities by himself/herself (Grade 1)" or "Disability that results in significant limitations during his/her daily life performance (Grade 2)" for the degree of the disability.

Generally, the cases with outpatient treatments alone are not applicable for relief benefits.

Improper purpose or improper use

The cases of "Improper purpose or improper use" basically include, regarding use of pharmaceuticals that caused adverse health effects, cases where the pharmaceuticals have been used in ways other than those approved by the Minister of the MHLW, or cases where the pharmaceuticals have not been used in accordance with the Precautions section in the package inserts.

For example, the following cases are considered as improper use and are not applicable for relief benefits if adverse health effects may occur.

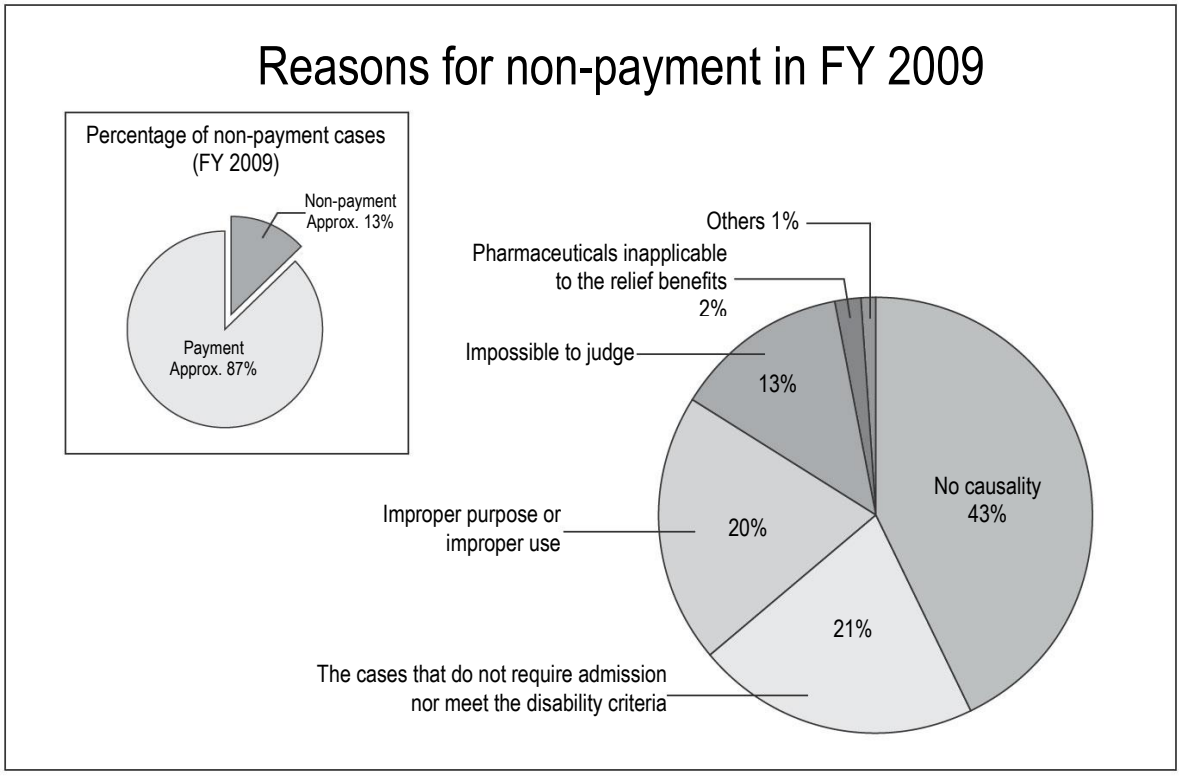
- In cases where necessary tests are not conducted without proper justification despite the package inserts include such Precautions that "for at least 2 months after initiating administration, physicians should be particularly alerted to the emergence of initial symptoms of adverse reactions. In principle, blood count (including differential white blood cell count) and

hepatic function tests should be performed once every 2 weeks…."

- In cases where the over-the-counter drugs (OTCs) such as common cold drugs or antipyretic analgesics are concomitantly used with other pharmaceuticals, although such use is prohibited in the package inserts of OTCs.

The Precautions section originally includes necessary information in order to ensure proper use and the safety of patients for whom pharmaceuticals are indicated. Please bear in mind, accordingly, that the Relief System for Sufferers may not be applied to the cases where pharmaceuticals are not used in accordance with the Precautions in the package inserts, even if adverse health effects occur.

In addition, cases where adverse reactions occur when patients take the pharmaceuticals which have been left without use (so called unused drug) by self-judgment without instruction of physicians are generally not applicable for the relief benefits since such cases are considered as improper use.



Impossible to judge

"Impossible to judge" refers to the cases where it cannot be judged based on the submitted documents whether there are causalities or whether pharmaceuticals are used for approved indications or in accordance with the instructions.

Pharmaceuticals not applicable to the relief benefits

"Pharmaceuticals not applicable to the relief benefits" refer to the cases where pharmaceuticals not applicable to the relief benefits are included in the causative drugs.

2

Summary of the Report on Adverse Reactions Associated with the Influenza A (H1N1) Vaccines in the 2009 Season

1. Introduction

Influenza A (H1N1) vaccines were provided to respond to the 2009 influenza as a part of the national vaccination program in accordance with the Notification by the MHLW, dated October 13, 2009, "Operating Procedure for Influenza A (H1N1) Vaccination at the Contract Medical Institutions"[1)] (Vaccination Operating Procedure).

To monitor the safety of the influenza A (H1N1) vaccines, the safety information have been intensively collected, in accordance with "Basic Policy of Influenza A (H1N1) Vaccination" (October 1, 2009) issued by the Japanese Government Task Force on Influenza A (H1N1) stating that, "(the vaccines) were the first vaccines against influenza A (H1N1), and its safety and efficacy have not been fully investigated. Therefore, extensive efforts, collecting and analyzing data, should be made to ensure the safety and efficacy of the vaccines and to improve the availability of safety and efficacy data to inform healthcare professionals and the general public." Accordingly, the Vaccination Operating Procedure clearly specifies the requirements to report adverse reactions which meet the "Adverse Reaction Reporting Criteria" to the MHLW regardless of causality as well as to define reporting obligations in the contract with medical institutions providing the vaccination services.

In accordance with the Vaccination Operating Procedure[1)], reported adverse reactions have been reviewed by the PMDA for causality etc. 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 Committee on Drug Safety Pharmaceutical Affairs and Food Sanitation Council and the Influenza A (H1N1) Vaccine Adverse Reaction Review Committee (the Joint Meeting) to determine the necessity of safety measures.

The summary of adverse reactions associated with the influenza A (H1N1) vaccines which were reported up to June 30, 2010 is presented below.

In addition, adverse reactions associated with the seasonal influenza vaccines which had been collected up to March 31, 2010 were identified and characterized. These adverse reactions, as well as those associated with the influenza A (H1N1) vaccines, were reviewed to determine whether an alert requiring a package insert revision should be issued. Details of the safety measures are also presented.

2. Adverse reactions associated with the influenza A (H1N1) vaccines reported in accordance with the Operating Procedure for Influenza A (H1N1) Vaccination at the Contract Medical Institutions (October 19, 2009 to June 30, 2010)

(1) Number of reported adverse reactions and reporting rates

Table 1 shows the number of adverse reactions associated with the influenza A (H1N1) vaccines reported by medical institutions and the reporting rates calculated from the estimated number of vaccinated persons based on the amount of vaccines distributed to the medical institutions.

Table 1

	Estimated number of vaccinated persons (number of vaccination)	Reported number of adverse reactions (reporting rates)	Number of reported serious cases (reporting rates)	Number of reported deaths (reporting rates)
Japanese domestic vaccines	22,833,137 (as of July 5, 2010)	2,428 (0.01%)	416 (0.002%)	133 (0.0006%)
Influenza A emulsion HA vaccine (H1N1 strain)	5,000 (as of July 5, 2010)	1 (0.02%)	0 (0.0%)	0 (0.0%)
Cell-culture derived influenza A emulsion HA vaccine (H1N1 strain)	2,550 (as of July 5, 2010)	4 (0.16%)	1 (0.04%)	0 (0.0%)

[unit: case (person)]

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

Number of adverse reactions to the influenza A (H1N1) vaccine reported by the medical institutions are shown by sex and age group in Tables 2 and 3.

Table 2

Sex	Reported number of adverse reactions
Male	769
Female	1,658 (39 pregnant women)
Unknown	6
Total	2,433

[unit: case (person)]

Table 3

Age	Reported number of adverse reactions	Reported number of serious cases	Reported number of deaths (%)
0 - 9	412	53	3 (2.2%)
10 - 19	96	13	1 (0.8%)
20 - 29	293	25	0 (0.0%)
30 - 39	427	35	3 (2.2%)
40 - 49	332	32	1 (0.8%)
50 - 59	248	29	4 (3.0%)
60 - 69	195	46	17 (12.8%)
70 - 79	243	90	38 (28.6%)
Aged 80 and older	181	94	66 (49.6%)
Unknown	6	0	0 (0.0%)
Total	2,433	417	133 (100%)

[unit: case (person)]

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

Table 4

Reporting period	Vaccination from October 19, 2009 to June 30, 2010		Total number of reports* (reporting rates)	Serious cases* (reporting rates)
Estimated number of vaccinated persons		Unit: 10,000 vaccinations		
Healthcare professionals Guardians of children under age of 1 Other than prioritized persons	Under age of 65	208.1 43.1 169.1	1,128 0.03%	59 0.001%
Healthcare professionals Others aged 65 and older	Aged 65 and older	11.2 270.4	181 0.006%	17 0.0006%
Persons with underlying diseases	Age of 1 to third graders in elementary school	90.1	116 0.01%	28 (including 2 fatalities) 0.003%
	Fourth to sixth graders in elementary school	16.4	10 0.01%	2 0.001%
	Junior high school and high school students or age equivalent to them	12.2	19 0.02%	2 0.002%
	High school graduates or people of an equivalent age to under age of 65	181.1	271 0.01%	84 (including 14 fatalities) 0.005%
	Aged 65 and older	429.6	343 0.008%	193 (including 116 fatalities) 0.004%
	Total	729.4	759 0.01%	309 0.004%
Pregnant women		45	38 0.0084%	6 0.0013%
Age of 1 to third graders in elementary school		516.6	308 0.006%	26 (including 1 fatality) 0.0005%
Fourth to sixth graders in elementary school		62.3	13 0.002%	0 0.000%
Junior high school and high school students or age equivalent to them		74.6	33 0.004%	5 0.0007%
Others		11.4		
Total		2,133.5	2,428 0.01%	416 (including 133 fatalities) 0.002%

* Reported adverse reactions associated with Japanese domestic vaccines [unit: case (person)]

(3) Specific topics of reported adverse reactions

A total of 151 cases of adverse reactions were identified as possible Guillain-Barre syndrome or acute disseminated encephalomyelitis (cases reported using the adverse reaction terms such as "numbness, feelings of weakness, neuropathy, muscular weakness, difficulty in swallowing" detailed in the Manuals for Management of Individual Serious Adverse Drug Reactions "Guillain-Barre syndrome"[2)]). Among the 151 cases, according to expert assessment, causality to the vaccines in 10 cases of Guillain-Barre syndrome and 5 cases of acute disseminated encephalomyelitis could not be denied.

A total of 121 cases of adverse reactions were reported as possible anaphylaxis (reported using the adverse reaction terms of anaphylaxis, anaphylactic reaction, anaphylactic shock, or anaphylactoid reaction). Fifty-five cases (30 serious cases) met Level 3 or higher of the "Brighton Criteria" [3)] (reporting rates of anaphylaxis was 0.2/100,000 vaccinations).

Nineteen cases of adverse reactions were reported as possible aggravation of interstitial pneumonia (the term interstitial pneumonia was used in the remarks section of the questionnaire prior to vaccination or in the description of clinical course, or as the adverse reaction term). Out of nineteen cases, according to expert assessment, the causality to vaccines in 7 cases could not be denied.

Table 5 presents a comparison of adverse reactions by system organ class between the seasonal influenza vaccines and the influenza A (H1N1) vaccines. The Table indicates the adverse reactions to the 2 types of vaccines were similar.

Table 5

System Organ Class of adverse reaction*	Number of adverse reactions	
	Seasonal influenza vaccines (FY 2006 to FY 2008)	Influenza A (H1N1) vaccines
Blood and lymphatic system disorders	15	4
Cardiac disorders	5	40
Ear and labyrinth disorders	3	6
Eye disorders	6	6
Gastrointestinal disorders	14	32
General disorders and administration site conditions	87	132
Hepatobiliary disorders	23	17
Immune system disorders	32	58
Infections and infestations	27	21
Injury, poisoning and procedural complications	1	0
Investigations	15	12
Metabolism and nutrition disorders	2	4
Musculoskeletal and connective tissue disorders	16	14
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0

Nervous system disorders	153	120
Psychiatric disorders	4	2
Renal and urinary disorders	6	4
Respiratory, thoracic and mediastinal disorders	33	68
Skin and subcutaneous tissue disorders	36	31
Endocrine disorders	0	1
Pregnancy, puerperium and perinatal conditions	0	2
Vascular disorders	24	12
Total	503	586

*Adverse reaction terms coded in accordance with the MedDRA/J Ver. 12.1

A total of 133 fatal cases were reported following vaccination. Most of them were elderly people with severe underlying diseases who were vaccinated in November and December. (**Table 3**)

In some cases, causality cannot be assessed due to limited information. However, according to the expert assessment, most fatal cases were probably caused by aggravation or recurrence of underlying diseases. They concluded that none of the deaths were directly associated with the vaccination. The vital statistics show death is quite frequent among elderly people with underlying diseases. Since all those who died after the vaccination had had severe underlying diseases, the vaccination may have been coincidentally followed by death. However, patients with severe underlying diseases should be carefully treated during and after vaccination since possibility that adverse reactions may cause serious outcomes cannot be totally ruled out in those patients.

3. Discussion about safety measures

Adverse reactions to the Japanese domestic influenza A (H1N1) vaccines have been reported to the MHLW since the start of the vaccination program on October 19, 2009 through March 31, 2010 and adverse reactions to the seasonal influenza vaccines reported to the PMDA from April 1, 2007 to March 31, 2010 were identified and characterized to determine whether the Precautions section should be revised.

Based on the accumulated adverse reaction reports and the causality assessment, the descriptions of interstitial pneumonia, thrombocytopenic purpura/decreased platelets and allergic purpura in the package insert needed to be amended to alert healthcare professionals for the following reasons.

The association between the influenza vaccination and interstitial pneumonia (including its aggravation) was unclear in many of the reports on interstitial pneumonia; e.g., some cases lack information such as pre- and post-vaccination images for assessment, while in others aggravation of interstitial pneumonia may have been triggered by pyrexia associated with the vaccination or incidental infections. However, several cases of interstitial pneumonia have been observed in which the causality could not be ruled out based on the temporal relationship between the vaccination and the onset of the adverse reaction. Some cases involved aggravation of interstitial pneumonia. Post-vaccination monitoring will be crucial for early detection of possible onset and aggravation of interstitial pneumonia. Therefore, the Precautions section was revised to provide information on interstitial pneumonia (including its aggravation).

Revision of the Precautions section describing thrombocytopenic purpura/decreased platelets

and allergic purpura was also considered appropriate since the causality could not be ruled out in some cases.

Table 6 presents the cases over the last 3 years for which causality could not be ruled out.

Table 6

	Influenza A (H1N1) vaccines (October 19, 2009 to March 31, 2010)	Seasonal influenza vaccines (April 1, 2007 to March 31, 2010)
Interstitial pneumonia	5 (including 4 cases of aggravation)	2 (including 1 case of aggravation)
Thrombocytopenic purpura Decreased platelets	0	9
Allergic purpura	1	5

Among other adverse reactions of which few cases are reported in Japan, it is considered that an alert should be also issued about adverse reactions for which alerts have been issued abroad in association with the inactivated influenza vaccines, although some of their manufacturing methods and ingredients are different to those of Japanese domestic and imported vaccines. The prescribing information about major inactivated influenza vaccines distributed in the United States were therefore reviewed.

As for encephalitis/encephalopathy and myelitis for which causality could not be ruled out, 2 cases of adverse reactions to the influenza A (H1N1) vaccines and 6 cases to the seasonal influenza vaccines were reported in the last 3 years. Since the overseas prescribing information alert healthcare professionals about the adverse reactions, the similar alerts should be included in the Japanese package inserts.

Regarding two imported vaccines, a small number of people were vaccinated compared with the Japanese domestic vaccines and only 1 case of serious adverse reaction to these vaccines has been reported since the approval in January 2010. Considering this and that the manufacturing methods and excipients of imported vaccines are different to the Japanese domestic vaccines, it is not known whether these adverse reaction trends are comparable. However, they are all inactivated vaccines consisting of influenza virus-derived antigens. Thus, it is expected that adverse reactions similar to those to the Japanese domestic vaccines may occur as more people are vaccinated with the imported vaccines. The risk of adverse reactions to imported vaccines should not be dismissed and inclusion of alerts in the package inserts of these vaccines is considered to be appropriate.

Thus, addition of information on interstitial pneumonia, thrombocytopenic purpura/decreased platelets, allergic purpura, encephalitis, encephalopathy, and myelitis in the package inserts of the influenza A (H1N1) vaccines and the seasonal influenza vaccines was determined to alert healthcare professionals. After the review at the Joint Meeting on August 25, 2010, instructions for revision of the Precautions section were issued to the marketing authorization holders on August 26, 2010[4)]

4. Safety measures hereafter

The 2010 Influenza A (H1N1) Vaccination Program was started in October 2010 in accordance with the Vaccination Operating Procedure.[1)] Medical institutions participating in the Vaccination Program are requested to carefully monitor adverse reactions to the influenza A (H1N1) vaccines and promptly report adverse reactions which meet the Adverse Reaction Reporting Criteria.

Collection of safety information such as adverse reaction reports and review of necessary safety measures need to be continued.

<References> (including provisionally translated titles)

1) Ministry of Health, Labour and Welfare: Operating Procedure for Influenza A (H1N1) Vaccination at Contract Medical Institutions (revised on October 1, 2010)

http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou04/pdf/youryou.pdf (only available in Japanese language)
2) Ministry of Health, Labour and Welfare: Manuals for Management of Individual Serious Adverse Drug Reaction (Guillain-Barre syndrome)
3) Ministry of Health, Labour and Welfare: Materials distributed at the 2010 Subcommittee on Drug Safety Committee on Drug Safety Pharmaceutical Affairs and Food Sanitation Council (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)
4) Revisions of the Precautions (instruction issued on August 26, 2010)
http://202.248.180.17/kaitei/kaitei20100826.html (only available in Japanese language)

3

Important Safety Information

This section presents contents of revisions and a case summary that served as the basis for these revisions to important adverse reactions included under the Precautions section of package inserts of drugs that have been revised in accordance with the Notification dated August 26 and September 16, 2010.

[Brand name]: Major product names are showed.

1 Influenza HA Vaccine, Influenza A (H1N1) HA Vaccine, Influenza A (H1N1) Emulsion HA Vaccine, Cell-culture Derived Influenza A (H1N1) Emulsion HA Vaccine

Brand Name (name of company)	**(1)Influenza HA Vaccine** Influenza HA Vaccine "KAKETSUKEN" TF (The Chemo-Sero-Therapeutic Research Institute) Influenza HA Vaccine "SEIKEN", Flu-Syringe "SEIKEN" (Denka Seiken Co., Ltd.) Influenza HA Vaccine "Hokken", Influenza HA Vaccine "S Hokken", Influenza HA Vaccine "S Hokken" Syringe (The Kitasato Institute) INFLUENZA HA VACCINE "BIKEN", FLUBIK HA, FLUBIK HA Syringe (The Research Foundation for Microbial Diseases of Osaka University) **(2) Influenza A (H1N1) HA Vaccine** Influenza A (H1N1) HA Vaccine "KAKETSUKEN" (The Chemo-Sero-Therapeutic Research Institute) Influenza A (H1N1) HA Vaccine "SEIKEN" (Denka Seiken Co., Ltd.) Influenza A (H1N1) HA Vaccine "BIKEN" (The Research Foundation for Microbial Diseases of Osaka University) Influenza A (H1N1) HA Vaccine "HOKKEN" (The Kitasato Institute) **(3) Influenza A (H1N1) Emulsion HA Vaccine** Arepanrix (H1N1) Intramuscular Injection (GlaxoSmithKline K.K.) **(4) Cell-culture Derived Influenza A (H1N1) Emulsion HA Vaccine** Cell-culture Derived Influenza A (H1N1) Emulsion HA Vaccine "Novartis" for Intramuscular Injection (Novartis Pharma K.K.)
Therapeutic Category	Vaccines
Indications	(1) and (2) Use for prevention of influenza. (3) and (4) Use for prevention of H1N1 influenza.

≪PRECAUTIONS (underlined parts are additions)≫

[Precautions (Persons requiring special cautions when considering vaccination)]	This vaccine should be given with caution in individuals <u>with respiratory disorders such as interstitial pneumonia and</u> bronchial asthma.
[Adverse Reactions	**<u>Thrombocytopenic purpura, decreased platelets</u>**: <u>Thrombocytopenic purpura</u>

(clinically significant adverse reactions)]

and decreased platelets may occur. If any abnormalities including purpura, epistaxis, and oral mucosa bleeding are observed, blood tests should be performed and appropriate measures should be taken.
Allergic purpura: Allergic purpura may occur. Patients should be carefully monitored, and if purpura or other symptoms occur, appropriate measures should be taken.
Interstitial pneumonia: Interstitial pneumonia may occur. Patients should be carefully monitored for clinical symptoms such as pyrexia, cough, and dyspnoea. If any abnormalities are observed, examinations including chest X-ray test should be performed, and appropriate measures should be taken.
Encephalitis/encephalopathy, myelitis: Encephalitis/encephalopathy, and/or myelitis may occur. Patients should be carefully monitored. If any abnormalities are observed, diagnosis should be made by MRI etc., and appropriate measures should be taken.

<Reference Information>

Influenza HA Vaccine
The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 3 years (April 2007 to March 2010)

- Thrombocytopenic purpura, decreased platelets: 9 cases (no fatalities)
- Allergic purpura: 5 cases (no fatalities)
- Interstitial pneumonia: 2 cases (including 1 fatality)
- Encephalitis/encephalopathy, myelitis: 6 cases (including 1 fatality)

Influenza A (H1N1) HA Vaccine
The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 6 months (October 2009 to March 2010)

- Thrombocytopenic purpura, decreased platelets: No case
- Allergic purpura: 1 case (no fatality)
- Interstitial pneumonia: 5 cases (including 3 fatalities)
- Encephalitis/encephalopathy, myelitis: 2 cases (no fatalities)

Influenza A (H1N1) Emulsion HA Vaccine
The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 3 months (from initial marketing to March 2010)

- Thrombocytopenic purpura, decreased platelets: No case
- Allergic purpura: No case
- Interstitial pneumonia: No case
- Encephalitis/encephalopathy, myelitis: No case

Cell-culture Derived Influenza A (H1N1) Emulsion HA Vaccine
The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past 2 months (from initial marketing to March 2010)

- Thrombocytopenic purpura, decreased platelets: No case
- Allergic purpura: No case
- Interstitial pneumonia: No case
- Encephalitis/encephalopathy, myelitis: No case

The number of individuals vaccinated for a year: Approximately 41.59 million for seasonal influenza vaccines (for FY 2009)

Approximately 22.83 million for H1N1 influenza vaccines (for FY 2009)
Marketed in Japan in:
September 1972 (Influenza HA Vaccine)
October 2009 (Influenza A (H1N1) HA Vaccine)
January 2010 (Influenza A (H1N1) Emulsion HA Vaccine)

Case Summary
<Influenza HA Vaccine>

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Male 70s	Immunization (periarteritis nodosa, chronic renal failure, hypertension, increased gamma-glutamyltransferase, increased blood creatinine)	0.5 mL Once	**Interstitial pneumonia** This patient had underlying interstitial pneumonia and a history of emphysema. Day of vaccination: The patient received an influenza HA vaccination at Hospital A. 1 day after vaccination: The patient visited the department of internal medicine of Hospital B with a chief complaint of general malaise. 2 days after vaccination: A blood test was performed showing increased white blood cells, CRP, BUN and creatinine. The patient's urinary protein also increased. He was admitted to the hospital to have a detailed examination and treatment. After admission, acute aggravation of interstitial pneumonia was suspected, but bacterial pneumonia was considered to be more likely. Treatment with intravenous infusion of tazobactam sodium/piperacillin sodium 2.25 g three times daily was started, but respiratory status, blood test and X-ray showed no improvement. 6 days after vaccination: Since chest CT showed exacerbation of interstitial opacity, pulse therapy with methylprednisolone 1 g/day (for 3 days) and oral administration of ciclosporin 100 mg/day were started. Antibiotic agent was switched from tazobactam sodium/piperacillin sodium to meropenem hydrate 0.5 g twice daily. Nevertheless, no improvement was noted. 9 days after vaccination: Since respiratory status worsened due to aspiration, the patient was fasted and received total parenteral nutrition and non-invasive positive pressure ventilation (NIPPV). Extracorporeal endotoxin-removal by direct hemoperfusion was performed twice starting from this day. The procedure was discontinued due to poor blood removal resulting from intravascular dehydration. Blood test results worsened with KL-6 1160 U/mL, SP-D 782 ng/mL, SPA 99.6 ng/mL, IL-2 < 0.8 pg/mL, IL-6 25.9 pg/mL and TNF-α 0.8 pg/mL. In addition, hepatic dysfunction was noted with AST (GOT) 39 IU/L and ALT (GPT) 124 IU/L, and administration of meropenem hydrate was thus discontinued.

				Mechanical ventilation was used. 12 days after vaccination: Respiratory status further worsened. Non-invasive positive pressure ventilation (NIPPV) was discontinued due to severe psychological stress and a strong complaint of agony, and respiratory management by an oxygen mask with reservoir bag at O_2 flow rate of 10 L/min was started. An X-ray showed gradual improvement of opacity in the right upper lung field, but respiratory status and arterial blood gas levels worsened. In addition, blood test showed increased FDP 34.7 μg/mL and D-dimer ≥25.0 μg/mL, and echocardiography showed a pattern of pulmonary hypertension. Therefore, pulmonary thromboembolism was suspected. 13 days after vaccination: CT angiography was performed, but no apparent thrombosis was found. Since fibrosis in both lung lower lobes worsened, a second course of methylprednisolone pulse therapy and administration of sivelestat sodium hydrate 100 mg/day and nafamostat mesilate 150 mg/day were started. 14 days after vaccination: Pulmonary perfusion scintigram was performed, but showed no apparent defect indicative of embolism. Respiratory status further worsened, resulting in a vicious circle where dyspnoea caused unrest, further aggravating respiratory status. 17 days after vaccination: Administration of propofol was started for sedation. 18 days after vaccination: Unrest became even more severe. Midazolam was concomitantly administered for sedation. Unrest improved but respiratory status continued to worsen. Blood pressure and heart rate began to decrease in the evening on this day. 19 days after vaccination: Heartbeat and breathing stopped, and there were no light reflexes. Then, death was confirmed (cause of death: respiratory failure). Autopsy result: interstitial pneumonia (Only 2 samples [2 × 2 cm] obtained from the left lung by left chest incision were observed.)
	Concomitant medications: nifedipine, losartan potassium, allopurinol, teprenone, ranitidine hydrochloride, doxazosin mesilate, dicyclomine hydrochloride/dried aluminum hydroxide gel/magnesium oxide			

Clinical Laboratory Values

	48 days before vaccination	1 day after vaccination	2 days after vaccination	3 days after vaccination	5 days after vaccination	6 days after vaccination	9 days after vaccination
WBC (/mm^3)	6400	11800	10600	8100	7000	9400	-
Eosinophils (%)	1	0	0	2	-	2	-
AST (GOT) (IU/L)	34	19	23	32	21	22	39
ALT (GPT) (IU/L)	17	10	11	13	21	22	124
LDH (IU/L)	243	230	232	236	199	265	-
CK (CPK) (IU/L)	1724	205	346	521	135	116	-
BUN (mg/dL)	31.8	28.5	31.2	27.2	19.0	15.0	-
CRP (mg/dL)	0.05	10.04	17.39	21.25	18.85	20.83	-
KL-6 (U/mL)	-	-	951	-	-	-	1160
SP-D (ng/mL)	-	-	506	-	-	-	782
SP-A (ng/mL)	-	-	105	-	-	-	99.6
IL-2 (pg/mL)	-	-	<0.8	-	-	-	<0.8
IL-6 (pg/mL)	-	-	21.9	-	-	-	25.9
TNF-α (pg/mL)	-	-	0.9	-	-	-	0.8
SpO_2 (%)	-	-	88-95	-	-	-	-

WBC: White blood cell count, AST (GOT):Aspartate aminotransferase (Glutamate oxaloacetate transferase), ALT (GPT): Alanine aminotransferase (Glutamate pyruvate transaminase), LDH: Lactate dehydrogenase, CK (CPK): Creatine kinase (Creatine phosphokinase), BUN: Blood urea nitrogen, CRP: C-reactive protein, KL-6: Sialylated carbohydrate antigen KL-6, SP-D: Surfactant protein D, SP-A: Surfactant protein A, IL-2: Interleukin-2, IL-6: Interleukin-6, TNF-α: Tumor necrosis factor-alfa, SpO_2: O_2 saturation

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 20s	Influenza immunization (none)	0.5 mL Once	**Idiopathic thrombocytopenic purpura** Day of vaccination: The patient received an influenza HA vaccination at workplace. Approximately 6 days after vaccination: Petechiae appeared on lower legs. It increased in number in 3 to 4 days, and purpura also occurred. 16 days after vaccination: The patient was examined for the first time at the department of hematology of other hospital. Platelet count was 0.4×10^4/mm^3, and severe petechiae and ecchymosis were noted predominantly on lower limbs. Oral mucosa bleeding was also noted. The patient was immediately admitted to the hospital. Since the patient also had pyrexia, decreased white blood cell and anaemia, bone marrow aspiration was also performed on this day. Based on the result, leukaemia and myelodysplastic syndrome were ruled out. PA-IgG markedly increased at 117.00 ng/10^7plts, and bone marrow findings were consistent with idiopathic thrombocytopenic purpura (ITP). Thus, the patient was diagnosed with acute ITP after vaccination. 18 days after vaccination: Dexamethasone pulse therapy (40 mg for 4 days) was started. Platelet count increased to the

				$12\times10^4/mm^3$ range, but immediately decreased to $0.6\times10^4/mm^3$. A total of 5 courses of dexamethasone pulse therapy were provided during hospitalization. 68 days after vaccination: The patient was discharged from the hospital. Platelet count was $6.9\times10^4/mm^3$ at the time of discharge. Prednisolone 10 mg/day was prescribed, and the patient was to be followed up on an outpatient basis. 72 days after vaccination: Purpura and petechiae on lower legs relapsed, and the patient visited the hospital. Platelet count was $0.4\times10^4/mm^3$. Dexamethasone pulse therapy was started on this day (sixth course). Administration of prednisolone was discontinued. 82 days after vaccination: Platelet count decreased again to $0.4\times10^4/mm^3$. A seventh course of dexamethasone pulse therapy was provided. Administration of cyclosporine 150 mg/day was started on the same day. 87 days after vaccination: Platelet count increased to $13.1\times10^4/mm^3$, but gradually decreased again. 96 days after vaccination: Platelet count was $1.1\times10^4/mm^3$, and prednisolone 15 mg/day was added to cyclosporine. 100 days after vaccination: Platelet count fluctuated between $7.4\times10^4/mm^3$ and $9.8\times10^4/mm^3$. Then, platelet count began to increase, and therefore dose reduction of cyclosporine was started. 299 days after vaccination: Platelet count was at the $16\times10^4/mm^3$ range when the patient visited the medical institution, and therefore dose reduction of prednisolone was started.
	Concomitant medications: none			

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Female Under age of 10	Influenza immunization (none)	0.2 mL Once	**Henoch-Schonlein purpura** The patient had no history of adverse drug reaction and allergic history. Day of vaccination: The patient received an influenza HA vaccine 0.2 mL (second administration). Approximately 30 days after vaccination: (exact day and time unknown) Purpura appeared under the left knee. The patient was left untreated and just monitored. Purpura repeatedly appeared and disappeared. 70 days after vaccination: The patient visited a dermatologist. 75 days after vaccination:

				The patient had arthralgia in the right leg (+). 77 days after vaccination: Purpura spread to both thighs. The patient was admitted to the hospital due to allergic purpura. The patient was kept at rest, and carbazochrome sodium sulfonate hydrate and ascorbic acid/calcium pantothenate were administered. Purpura gradually resolved, and ankle swelling disappeared. Tenderness also disappeared. 81 days after vaccination: The patient was discharged from the hospital. The patient was then followed up on an outpatient basis. Purpura repeatedly appeared and disappeared, but urine analysis showed no abnormality. No joint swelling was noted. The patient is currently followed up with administration of carbazochrome sodium sulfonate hydrate and ascorbic acid/calcium pantothenate.
	Concomitant medications: none			

Clinical Laboratory Values

	77 days after vaccination:
RBC (× 10^4/mm^3)	481
Hemoglobin (g/dL)	12.8
Hematocrit (%)	38.8
WBC (/mm^3)	8510
Stab cell (%)	3.0
Segmented cell (%)	50.0
Eosinophils (%)	1.0
Basophils (%)	1.0
Lymphocytes (%)	41.0
Monocytes (%)	4.0
PLT(×10^4/mm^3)	32.3
Amylase (IU/L)	44
CRP (mg/dL)	0.0
ESR	54
DLST (this drug)	786 S.I (%) positive

RBC: Red blood cell count, WBC: White blood cell count, PLT: Platelet, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Male 70s	Immunization (none)	0.5 mL Once	**Acute cerebellitis** The patient had a history of rheumatoid arthritis for 8 years. Day of vaccination: The patient received an influenza HA vaccination at Hospital A.

				2 days after vaccination: The patient visited Hospital B for chills, shivering and pyrexia. 6 days after vaccination: The patient was admitted to the hospital due to increased inflammatory reaction and treated with antibiotics. Date unknown: The patient was transferred to Hospital A because no improvement was observed. 10 days after vaccination: Lumbar puncture was performed because of progressive weakness of lower extremities, intention tremor and disturbances in consciousness, and detailed examination was performed for suspected viral encephalitis and acute disseminated encephalomyelitis (ADEM). Blood test showed no dominant viral infection, and imaging test showed no evidence of demyelination. The patient was thus diagnosed with acute cerebellitis. Date unknown: The symptoms markedly improved through steroid pulse therapy. The patient was discharged from the hospital.
	Concomitant medications: unknown			

WBC (/mm^3)	8510
Stab cell (%)	3.0
Segmented cell (%)	50.0
Eosinophils (%)	1.0
Basophils (%)	1.0
Lymphocytes (%)	41.0
Monocytes (%)	4.0
PLT(×10^4/mm^3)	32.3
Amylase (IU/L)	44
CRP (mg/dL)	0.0
ESR	54
DLST (this drug)	786 S.I (%) positive

RBC: Red blood cell count, WBC: White blood cell count, PLT: Platelet, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
4	Male 70s	Immunization (none)	0.5 mL Once	**Acute cerebellitis** The patient had a history of rheumatoid arthritis for 8 years. Day of vaccination: The patient received an influenza HA vaccination at Hospital A. 2 days after vaccination:

				The patient visited Hospital B for chills, shivering and pyrexia. 6 days after vaccination: The patient was admitted to the hospital due to increased inflammatory reaction and treated with antibiotics. Date unknown: The patient was transferred to Hospital A because no improvement was achieved. 10 days after vaccination: Lumbar puncture was performed because of progressive weakness of lower extremities, intention tremor and disturbances in consciousness, and detailed examination was performed for suspected viral encephalitis and acute disseminated encephalomyelitis (ADEM). Blood test showed no dominant viral infection, and imaging test showed no evidence of demyelination. The patient was thus diagnosed with acute cerebellitis. Date unknown: The symptoms markedly improved through steroid pulse therapy. The patient was discharged from the hospital.
	Concomitant medications: unknown			

2 Thalidomide

Brand Name (name of company)	THALED CAPSULE 50, 100 (Fujimoto Pharmaceutical Corporation)
Therapeutic Category	Antineoplastics-Miscellaneous
Indications	Relapsed or refractory multiple myeloma

≪PRECAUTIONS (underlined parts are additions)≫

[WARNING]

WARNING

In administering this drug to women with child-bearing potential, a pregnancy test must be performed in advance, and administration should be started only when a negative test result has been confirmed. It must be assured that both the patient and his/her partner, if engaged in sexual activity, take maximally effective contraceptive measures (men must use condoms) during the period between 4 weeks before start of administration and 4 weeks after completion of administration, and physicians should thoroughly confirm their compliance and periodically conduct pregnancy tests.

The patients must be instructed to immediately discontinue taking this drug and to consult physicians when pregnancy is suspected.

This product is secreted into seminal fluid. Therefore, when administering this drug to male patients, they must be instructed to, if they engage in sexual activity, take maximally effective contraceptive measures (men must use condoms) during the period between start of administration and 4 weeks after completion of administration, and physicians should thoroughly confirm their compliance. They should also be instructed not to engage in sexual activity with pregnant women during this period.

[Important Precautions]

Patients should be instructed not to provide their sperm/semen during the period between start of administration and 4 weeks after completion of administration.

[Adverse Reactions (clinically significant adverse reactions)]	**Infection**: Serious infections including pneumonia may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.
[Use in Pregnant, Parturient And Nursing Women]	Breast-feeding must be discontinued when this drug is administered to nursing mothers. Breast-feeding must be discontinued until 4 weeks after completion of administration.
<Reference Information>	The number of reported adverse reactions (for which a causality to the drug could not be denied) for the past one and a half years (from initial marketing to September 2010) • Infectious diseases: 10 cases (no fatalities) The number of patients treated with this drug per year estimated by marketing authorization holder (MAH): approximately 2,200 (2009) Marketed in Japan in: February 2009 (THALED CAPSULE 100), May 2010 (THALED CAPSULE 50)

Case Summary

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
1	Female 60s	Multiple myeloma (constipation, reflux oesophagitis, osteoporosis, hypokalaemia)	100 mg for 27 days ↓ (administration suspended for 7 days) ↓ 100 mg for 16 days	**Pneumonia** Approximately 11months before administration: The patient developed multiple myeloma. Approximately 10 months before administration: MCNU-VMP [MCNU (ranimustine), vindesine, melphalan, and prednisolone]therapy was performed (for approximately 2 months). Approximately 8 months before administration: Administration of dexamethasone and bortezomib was started (administered for approximately 4 months). Approximately 4 months before administration: MP (melphalan and prednisolone) therapy was performed (for approximately 3 months). Approximately 1 months before administration: Administration of prednisolone was started (administered for approximately 1 month). Day 1 of administration: Administration of thalidomide was initiated at 100 mg. Day 28 of administration (day of discontinuation): Non-serious pneumonia developed. Administration of thalidomide was temporarily discontinued. 1 day after discontinuation: Cefepime dihydrochloride hydrate was administered. 2 days after discontinuation: Faropenem sodium hydrate was administered. 5 days after discontinuation: The patient recovered. 8 days after discontinuation (day of readministration): Administration of thalidomide was resumed at 100 mg. Day 6 of readministration: Serious pneumonia developed. Day 7 of readministration: Ceftriaxone sodium hydrate was administered. Oxygen inhalation was performed. Day 14 of readministration:

				The patient recovered. Day 17 of readministration: (day of discontinuation of readministration) Serious pneumonia recurred. Administration of thalidomide was discontinued. Sulbactam sodium/ampicillin sodium was administered. Oxygen inhalation was performed. 12 days after discontinuation of readministration: The patient recovered.
	Concomitant medications: sodium rabeprazole, pantethine, potassium L-aspartate, senna leaf/senna fruit, alendronate sodium hydrate, rebamipide, meloxicam, magnesium oxide, mosapride citrate hydrate, morphine sulfate hydrate, aspirin, prochlorperazine maleate, furosemide			

Clinical Laboratory Values

	Day 1 of administration	2 days after discontinuation	Day 8 of readministration	1 day after discontinuation of readministration	2 days after discontinuation of readministration	20 days after discontinuation of readministration
WBC (/mm^3)	3400	4100	4000	4200	7300	4800
Neutrophils (%)	67.9	69.5	79.2	61.6	82.3	65.3
Lymphocytes (%)	22.8	13.8	15.3	33.3	10.6	24.4
Monocytes (%)	8.2	15	3.8	2.6	5	7.5
Eosinophils (%)	0.8	0.7	1.3	2	2	1.7
Basophils (%)	0.3	1	0.4	0.5	0.1	1.1
CRP (mg/dL)	-	3.1	8.6	2.5	12.2	0.1

WBC: White blood cell count, CRP: C-reactive protein

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
2	Female 60s	Multiple myeloma (none)	100 mg for 23 days ↓ (administration suspended for 2 days) ↓ 100 mg continued	**Easily infectible condition (pneumonia)** Approximately 1 years and 6 months before administration: The patient developed multiple myeloma. Approximately 1 years and 5 months before administration: VAD (vincristine, doxorubicin and dexamethasone) therapy was performed (for approximately 2 months). Approximately 1 years and 3 months before administration: Administration of cyclophosphamide was started (administered for approximately 1 month). Approximately 1 years before administration: Administration of high-dose melphalan and autologous peripheral blood stem cell transplantation were performed (first attempt). Approximately 9 months before administration: Administration of high-dose melphalan and autologous peripheral blood stem cell transplantation were performed (second attempt). Day 1 of administration: Administration of thalidomide was initiated at 100 mg. Day 24 of administration (day of discontinuation): Easily infectible condition (pneumonia) developed. Administration of thalidomide was temporarily discontinued. Cefepime dihydrochloride hydrate was administered. 2 days after discontinuation (day of readministration): Since easily infectible condition (pneumonia) was tended

				to improve, administration of thalidomide was resumed at 100 mg. Day 11 of readministration: The patient recovered.
	Concomitant medications: brotizolam, dextromethorphan hydrobromide hydrate, magnesium oxide			

Clinical Laboratory Values

	14 days before administration	Day 13 of administration	Day 24 of administration (day of discontinuation)	2 days after discontinuation (day of readministration)	Day 11 of readministration
WBC (/mm^3)	5470	3950	6700	3380	5920
Neutrophils (%)	71	57	-	67	66
Lymphocytes (%)	20	25	-	15	22
Monocytes (%)	4	14	-	12	7
Eosinophils (%)	3	3	-	3	2
Basophils (%)	0	-	-	1	1

WBC: White blood cell count

No.	Patient		Daily dose/ Treatment duration	Adverse reactions
	Sex/ Age	Reason for use (complications)		Clinical course and therapeutic measures
3	Male 70s	Multiple myeloma (none)	100 mg for 16 days	**Pneumococcal pneumonia** Approximately 2 years and 2 months before administration: The patient developed multiple myeloma. MP (melphalan and prednisolone) therapy was provided (for approximately 5 months). Approximately 1 years and 9 months before administration: CP (cyclophosphamide and prednisolone) therapy was provided (for approximately 1 year). Approximately 7 months before administration: Administration of bortezomib was started (administered for approximately 7 months). Day 1 of administration: Administration of thalidomide was initiated at 100 mg. Day 17 of administration (day of discontinuation) Pneumococcal pneumonia developed. Administration of thalidomide was discontinued. Ceftriaxone sodium hydrate was administered. 19 days after discontinuation: Symptoms remitted.
	Concomitant medications: prednisolone, amlodipine besilate, meloxicam, famotidine, brotizolam			

Clinical Laboratory Values

	13 days before administration	Day 14 of administration	Day 17 of administration (day of discontinuation)	11 days after discontinuation
WBC (/mm^3)	2700	2100	1100	2200
Neutrophils (/mm^3)	1491	1089	378	1259
Lymphocytes (/mm^3)	1009	780	-	-
Monocytes (/mm^3)	209	201	-	-
Eosinophils (/mm^3)	11	21	-	-
Basophils (/mm^3)	0	0	-	-

WBC: White blood cell count

4

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 collects the adverse drug reactions (ADRs) in all of the medical institutions where the drugs are used and takes safety measures. The aim of the EPPV is to promote the rational use of the drug in medical treatments, and to take prompt actions for the prevention of the serious adverse drug reactions.

EPPV is specified as a condition of approval.

(As of October 1, 2010)

Nonproprietary name Brand name on	Name of the marketing authorization holder	Date of EPPV initiate
Everolimus AFINITOR tablets 5 mg	Novartis Pharma K.K.	March 8, 2010
Rasburicase (Genetical Recombinant) Rasuritek for I.V. Injection 1.5 mg, 7.5 mg	Sanofi-aventis K.K	April 5, 2010
Olmesartan Medoxomil/Azelnidipine REZALTAS COMBINATION TABLETS LD, HD	Daiichi Sankyo Company, Limited.	April 16, 2010
Valsartan/Amlodipine Besilate EXFORGE Combination Tablets	Novartis Pharma K.K.	April 16, 2010
Vildagliptin Equa Tablets 50 mg	Novartis Pharma K.K.	April 16, 2010
Sugammadex Sodium Bridion Intravenous 200 mg, 500 mg	Schering-Plough K.K.	April 19, 2010
Duloxetine Hydrochloride Cymbalta Capsule 20 mg, 30 mg	Shionogi & Co., Ltd.	April 19, 2010
Latanoprost/Timolol Maleate Xalacom Combination Eye Drops	Pfizer Japan Inc.	April 20, 2010
Palonosetron Hydrochloride ALOXI I.V. Injection 0.75 mg	Taiho Pharmaceutical Co., Ltd.	April 22, 2010
Metformin Hydrochloride Metgluco Tablets 250 mg	Dainippon Sumitomo Pharma Co., Ltd.	May 10, 2010
Thalidomide THALED capsule 50	Fujimoto Pharmaceutical Corporation	May 25, 2010
Epoetin Kappa (Genetical Recombinant) [Epoetin Alfa Biosimilar 1] Epoetin Alfa BS Injection 750 syringe [JCR], Epoetin Alfa BS Injection 1500 syringe [JCR], Epoetin Alfa Injection 3000 syringe [JCR], Epoetin Alfa BS Injection 750 [JCR], 1500 [JCR], 3000 [JCR]	JCR Pharmaceuticals Co., Ltd.	May 27, 2010
Travoprost/Timolol Maleate DuoTrav Combination Ophthalmic Solution	Alcon Japan Ltd.	June 11, 2010

Dorzolamide Hydrochloride/Timolol Maleate COSOPT Ophtalmic Solution	Banyu Pharmaceutical Co., Ltd.	June 11, 2010
Eculizumab (Genetical Recombination) Soliris Intravenous Drip Infusion 300 mg	Alexion Pharmaceuticals, Inc.	June 14, 2010
Alogliptin Benzoate NESINA Tablets 6.25 mg., 12.5 mg., 25 mg.	Takeda Pharmaceutical Company Limited	June 15, 2010
Candesartan Cilexetil/Amlodipine Besilate UNISIA Combination Tablets LD, HD	Takeda Pharmaceutical Company Limited	June 15, 2010
Panitumumab (Genetical Recombination) Vectibix Intravenous Drip Infusion 100 mg	Takeda Pharmaceutical Company Limited	June 15, 2010
Pregabalin Lyrica Capsules 25 mg, 75 mg, 150 mg	Pfizer Japan Inc.	June 22, 2010
Fentanyl Citrate Fentos Tape 1 mg, 2 mg, 4 mg, 6 mg, 8 mg	Hisamitsu Pharmaceutical Co., Inc.	June 24, 2010
Metformin Hydrochloride/Pioglitazone Hydrochloride METACT Combination Tablets LD, HD	Takeda Pharmaceutical Company Limited	July 6, 2010
Ramelteon ROZEREM Tablets 8 mg	Takeda Pharmaceutical Company Limited	July 6, 2010
Lenalidomide Hydrate Revlimid Capsules 5 mg	Celgene K.K.	July 20, 2010*[1] August 20, 2010*[2]
Olopatadine Hydrochloride ALLELOCK Tablets 2.5, 5*[3]	Kyowa Hakko Kirin Co., Ltd.	July 23, 2010
Pazufloxacin Mesilate PASIL INTRAVENOUS DRIP INFUSION 300 mg, 500 mg*[4]	Toyama Chemical Co., Ltd.	July 23, 2010
Pazufloxacin Mesilate Pazucross INJECTION 300, 500*[4]	Mitsubishi Tanabe Pharma Corporation	July 23, 2010
Budesonide Pulmicort 100 µg Turbuhaler 112 doses, Pulmicort 200 µg Turbuhaler 56, 112 doses*[5]	AstraZeneca K.K.	July 23, 2010
Lansoprazole Takepron capsules 15, Takepron OD Tablets 15	Takeda Pharmaceutical Company Limited	July 23, 2010*[6] August 20, 2010*[7]
Darbepoetin Alfa (Genetical Recombination) NESP INJECTION 10 µg/1 mL PLASTIC SYRINGE, NEPS INJECTION 15 µg/1 mL PLASTIC SYRINGE, NESP 20 µg/1 mL PLASTIC SYRINGE, NESP INJECTION 30 µg/1 mL PLASTIC SYRINGE, NESP INJECTION 40 µg/1 mL PLASTIC SYRINGE, NEPS INJECTION 60 µg/0.6 mL PLASTIC SYRINGE, NESP 120 µg/0.6 mL PLASTIC SYRINGE, NESP INJECTION 180 µg/0.9 mL PLASTIC SYRINGE	Kyowa Hakko Kirin Co., Ltd.	August 26, 2010
Ambrisentan Volibris Tablets 2.5 mg	GlaxoSmithKline K.K.	September 17, 2010
Tramadol Hydrochloride Tramal Capsules 25 mg, 50 mg	Nippon Shinyaku Co., Ltd.	September 17, 2010
Levetiracetam E Keppra Tablets 250 mg, 500 mg	UCB Japan Co., Ltd.	September 17, 2010
Abatacept (Genetical Recombination) ORENCIA FOR I.V. INFUSION 250 mg	Bristol-Myers K.K.	September 21, 2010

Temsirolimus TORISEL Injection 25 mg	Pfizer Japan Inc.	September 22, 2010
Paclitaxel Abraxane I.V. Infusion 100 mg	Taiho Pharmaceutical Co., Ltd.	September 24, 2010

*1 The originally approved indication for "treatment of patients with relapsed or refractory multiple myeloma"

*2 An additional indication for "treatment of patients with myelodysplastic syndrome associated with a chromosome 5q deletion"

*3 An additional administration for "pediatrics (aged 7 and older)"

*4 An additional indication for "treatment of patients with sepsis, applicable microorganism; *Streptococcus pneumonia*"

*5 An additional administration for "pediatrics"

*6 An additional indication for "treatment of patients with suppression of recurrent gastric or duodenal ulcer associated with administration of low-dose aspirin"

*7 An additional indication for "treatment of patients with suppression of recurrent gastric or duodenal ulcer associated with administration of non-steroidal anti-inflammatory drugs"

Reports on adverse reactions associated with seasonal influenza vaccines in FY 2009 (Results of the report of the Vaccine Adverse Reaction Review Committee)

The reports on adverse reactions associated with seasonal influenza vaccines since FY 2003 have been described in Pharmaceuticals and Medical Devices Safety Information. This section summarizes reports on adverse reactions associated with seasonal influenza vaccines in FY 2009. **Table 1** indicates the estimated amount of influenza vaccines shipped, number of adverse reaction reports, and number of adverse reaction events reported in the past 5 years. **Table 2** shows the number of adverse reactions associated with seasonal influenza vaccines in 2009 according to age group, sex and outcome. **Table 3** and **4** show the narrative case summaries and the causality assessments by the Vaccine Adverse Reaction Review Committee, consisting of experts in infections and viruses, for the cases of deaths or sequelae in FY 2009, respectively.

Table 5 shows numbers of adverse reactions associated with the seasonal influenza vaccination reported in FY 2009 (cases reported regardless of causality) under the Vaccine Adverse Reaction Reporting System (Note 2) as reference.

Table 1 Estimated Amounts of Seasonal Influenza Vaccines Shipped, Number of Adverse Reaction Cases, and Number of Adverse Reactions in the Past 5 Years

	FY 2005	FY 2006	FY 2007	FY 2008	FY 2009
Estimated amount of vaccines shipped	Approx. 19.32 million vials	Approx. 18.77 million vials	Approx. 22.57 million vials	Approx. 24.51 million vials	Approx. 20.39 million vials
Estimated number of vaccines	Approx. 37.55 million	Approx. 35.59 million	Approx. 41.64 million	Approx. 47.40 million	Approx. 41.59 million
Number of adverse reaction cases	102	107	122	121	120
Number of adverse reactions	139	149	190	166	162

Table 2 Reported Cases of Adverse Reaction Associated with Seasonal Influenza Vaccines by Age Group, Sex, and outcome

	Total			Recovered/Improved			Unrecovered		Unknown			Sequelae		Deaths	
	Male	Female	Sex unknown	Male	Female	Sex unknown	Male	Female	Male	Female	Sex unknown	Male	Female	Male	Female
Number of reported cases	120			68			14		26			3 (0)		9 (1)	
	60	56	4	38	29	1	7	7	10	13	3		3 (0)	5 (1)	4 (0)
Under age of 10	34			27					7						
	21	13		19	8				2	5					
10 to 19 years	8			7			1								
	2	6		2	5			1							
20 to 29 years	7			5			1		1						
	2	4	1	1	3	1		1	1						
30 to 39 years	9			3			4		2						
	5	4		1	2		3	1	1	1					
40 to 49 years	14			5			1		5			1 (0)		2 (0)	
	7	7		3	2			1	4	1			1 (0)		2 (0)
50 to 59 years	6			4			1					1 (0)			
	3	3		3	1			1					1 (0)		
60 to 69 years	6			4			2								
	3	3		1	3		2								
70 to 79 years	19			7			3		4			1 (0)		4 (1)	
	8	10	1	3	4		2	1		3	1		1 (0)	3 (1)	1 (0)
80 to 89 years	14			5			1		5					3 (0)	
	8	6		4	1			1	2	3				2 (0)	1 (0)
Unknown	3			1					2						
	1		2	1							2				

(Note)
1. Number in parenthesis indicates cases of "Sequelae" and "Deaths," where causality between the reported adverse reaction and influenza vaccination could not be ruled out.
2. Counting overlapped when reported by multiple companies.

Table 3 Summary of Death Cases

No.	Case Summary	Review results of the Review Committee
1	Female in her 80s Adverse reactions: cardio-respiratory arrest Past history/complications: hepatic encephalopathy (primary disease), hepatitis C (primary disease), hyperammonaemia (complication), senile dementia (primary disease), subarachnoid haemorrhage (past history), frontotemporal dementia (primary disease) The patient received a seasonal influenza vaccination. One day after vaccination, she was admitted to a nursing care facility. At midnight 2 days after vaccination, the nursing care facility contacted the hospital and told that the patient's condition suddenly changed and led to cardio-respiratory arrest.	In this case, the patient's condition suddenly changed 2 days after vaccination and eventually led to death. Causality to the influenza vaccination could not be evaluated since there was limited information available on the clinical course from vaccination to death and on details at the time of death.

	In the early morning, the patient was found in cardio-respiratory arrest with bloody vomit. She was immediately taken to a medical institution and received emergency medical treatment, but she died eventually (the cause of death was unknown).	
2	Male in his 80s Adverse reactions: cardio-respiratory arrest Past history/complications: angina pectoris (past history), diverticulitis (past history) The patient received a seasonal influenza vaccination and returned home. Four hours after vaccination, the patient's wife called home from an outside location and talked with him, reporting that he was in good condition. Six hours after vaccination, the wife called home but nobody answered. Seven hours after vaccination, the wife returned home and found him lying in a back room. His body was warm. Since the pulse was not palpable and he was in respiratory arrest, he was taken to a medical institution by ambulance. Then, his death was confirmed.	In this case, the patient's condition suddenly changed after vaccination and eventually led to sudden death. Causality to the influenza vaccination could not be evaluated since there was limited information available on the clinical course from vaccination to death and on details at the time of death.
3	Male in his 70s Adverse reactions: death Past history/complications: cervical spinal stenosis (past history), diabetes mellitus (primary disease), hypertension (primary disease) The patient had underlying diabetes mellitus (uncontrolled) and hypertension, and a history of cervical spinal stenosis. He had a history of seasonal influenza vaccination 1 year and 2 years earlier. No adverse reactions occurred at those times. The patient received a seasonal influenza vaccination, and on the following morning, he was found dead in his bed (the cause of death was unknown).	In this case, the patient with underlying cervical spinal stenosis, hypertension, and uncontrolled diabetes mellitus died on the following day of vaccination. Causality to the influenza vaccination could not be evaluated since there was limited information available on the clinical course from vaccination to death and on details at the time of death.
4	Male in his 80s Adverse reactions: pyrexia Past history/complications: atrial fibrillation, cerebral infarction (past history), pancytopenia, quadriplegia The patient was unable to walk, stand and remain seated with a history of 2 episodes of multiple cerebral infarction. He received treatment with total parenteral nutrition and underwent gastrostomy due to repeated aspiration pneumonia. One month before vaccination for seasonal influenza, he experienced severe anaemia and decreased white blood cell. Eight days before vaccination for seasonal influenza, he received influenza A (H1N1) vaccination. No abnormalities were observed. He received seasonal influenza vaccine. At midnight on the day of vaccination, pyrexia in the 38°C range occurred. Two days after vaccination, pyrexia in the 37°C range persisted. Three days after vaccination, wheezing, and polypnoea occurred. In the morning 4 days after vaccination, the patient had respiratory arrest and died. Remarks: The patient received an influenza A (H1N1)	In this case, the patient, who (1) required prolonged bed rest, (2) received total parenteral nutrition and gastrostomy due to repeated aspiration pneumonia, and (3) experienced anaemia and decreased white blood cell, died 4 days after seasonal influenza vaccination. The causality between vaccination and pyrexia could not be ruled out since pyrexia occurred on the day of vaccination. However, the causality between vaccination and death was unknown and could not be evaluated since aspiration pneumonia might have resulted in respiratory arrest.

	vaccination.	
5	Male in his 70s Adverse reactions: acute respiratory failure, interstitial pneumonia Past history/complications: polyarteritis nodosa (primary disease), emphysema (past history), chronic renal failure (primary disease), hypertension (primary disease), interstitial pneumonia (primary disease), increased gamma-glutamyltransferase (complication), increased blood creatinine (complication) The patient had been followed up as an outpatient for periarteritis nodosa, chronic renal failure, and hypertension. He had underlying interstitial pneumonia and a history of emphysema. He received seasonal influenza vaccination. In the morning 1 day after vaccination, he visited the hospital with a chief complaint of general malaise. Acute respiratory failure and interstitial pneumonia developed. In the morning 2 days after vaccination, a blood test revealed increased white blood cells, CRP, BUN and creatinine. His urinary protein also increased. The patient was admitted to the hospital to have a detailed examination and treatment. After admission, acute aggravation of interstitial pneumonia was suspected, but it was concluded that bacterial pneumonia was more likely. Empiric treatment with intravenous infusion of tazobactam sodium/piperacillin sodium was started, but respiratory status, blood test and X-ray showed no improvement. In the morning 3 days after vaccination, his respiratory status worsened. Six days after vaccination, since chest CT showed exacerbation of interstitial opacity, steroid pulse therapy and oral administration of ciclosporin were started. The antibiotic agent was switched to meropenem hydrate. Nevertheless, no improvement was noted. Nine days after vaccination, since respiratory status worsened due to aspiration, the patient was fasted and received total parenteral nutrition and non-invasive positive pressure ventilation (NIPPV). Extracorporeal endotoxin-removal by direct hemoperfusion was performed twice on this day The procedure was discontinued due to poor blood removal resulting from intravascular dehydration. A blood test showed that his condition had worsened. In addition, hepatic dysfunction was noted, and administration of meropenem hydrate was thus discontinued. Mechanical ventilation was used at midnight on the same day. Twelve days after vaccination, respiratory status further worsened. NIPPV was discontinued due to severe psychological stress and a strong complaint of agony, and respiratory management by an oxygen mask with a reservoir bag was started. An X-ray showed gradual improvement of opacity in the right upper lung field, but respiratory status and arterial blood gas pattern worsened. As a result of a blood test, pulmonary thromboembolism was suspected. Thirteen days after vaccination, CT angiography showed no apparent thrombosis. Since fibrosis in both lung lower lobes	In this case, the patient who had underlying periarteritis nodosa, emphysema, interstitial pneumonia, chronic renal failure, and hypertension, died of respiratory failure 19 days after vaccination. Bacterial pneumonia or underlying illnesses might be associated with the adverse reactions because the patient's respiratory status worsened within a few days after vaccination. Meanwhile, the causality between vaccination and death could not be ruled out because the series of the course resulting in death occurred after vaccination. However, it was difficult to evaluate the causality due to insufficient information.

	worsened, a second course of steroid pulse therapy and administration of sivelestat sodium hydrate and nafamostat mesilate were started. Fourteen days after vaccination, pulmonary perfusion scintigram was performed, but showed no apparent defect suggestive of embolism. Seventeen days after vaccination, administration of propofol was started for sedation. Eighteen days after vaccination, unrest became even more severe, and midazolam injection was concomitantly administered for sedation. Unrest improved but respiratory status worsened. Blood pressure and heart rate began to decrease in the evening on this day. At midnight 19 days after vaccination, the heartbeat and breathing stopped, and there were no light reflexes. Then, death was confirmed (cause of death: respiratory failure). Only 2 samples (2 × 2 cm) were obtained from the left lung by left chest incision (autopsy result: only partial lung was observed, interstitial pneumonia).	
6	Female in her 70s Adverse reactions: near drowning Past history/complications: hepatic malignant neoplasm (complication) As there were no abnormal findings on examination using a questionnaire etc., the patient received a seasonal influenza vaccination. No abnormalities were noted after vaccination, and she returned home. Six and a half hours after vaccination, she was found drowning in a bathroom by her family member,. She was taken to a hospital by ambulance but did not respond to resuscitation. Seven and a half hours after vaccination, her death was confirmed. A large amount of water was found in the trachea. She was diagnosed with acute cardiac failure based on her age.	In this case the patient suddenly died 7 and a half hours after vaccination. Causality to the influenza vaccination could not be evaluated since there was limited information available on the clinical course from vaccination to death and on details at the time of death.
7	Male in his 70s Adverse reactions: pyrexia, rash generalised, abnormal hepatic function Past history/complications: multiple recurrent cerebral infarction (past history), Parkinson's syndrome, abnormal renal function (past history), dysphagia, renal failure, pneumonia, hypertension The patient had been hospitalized for treatment of a sequela of multiple recurrent cerebral infarction, chronic renal failure, dysphagia, pneumonia, hypertension, and Parkinson's syndrome. He had been followed up mainly for chronic renal failure, dysphagia due to the sequela of multiple recurrent cerebral infarction, and relapsing pneumonia. As his pneumonia was improving, his discharge was planned. The patient received a seasonal influenza vaccination. Ten days after vaccination, the patient received an influenza A (H1N1) vaccination. Fifteen days after vaccination, generalised exanthema was noted (with itchy skin). Sixteen days after vaccination, pyrexia over 38.5°C occurred, and generalised exanthema worsened. Meropenem	In this case, the patient developed skin symptoms such as rash 15 days after vaccination, followed by worsening of respiratory symptoms with pneumonia on CT and died 20 days after vaccination. Pneumonia was tended to improve prior to vaccination, but pyrexia and the series of clinical symptoms occurred after vaccination. Therefore, the causality between vaccination and pyrexia could not be ruled out, but causality between vaccination and death was unknown and could not be evaluated.

	hydrate for injection was administered, but pyrexia did not resolve. A topical cream was prescribed for skin symptoms. Seventeen days after vaccination, pyrexia of 37.0°C or more persisted. An antiallergic agent was administered for skin symptoms. Eighteen days after vaccination, pyrexia of 38.0°C or more recurred. While the worsening of skin symptoms persisted, chest CT showed pneumonia. A blood test showed increased white blood cell count 13640/mm^3, CRP 32.82 mg/dL, AST (GOT) 220 IU/L, ALT (GPT) 88 IU/L, LDH 403 IU/L, ACP 459 IU/L, BUN 74.0 mg/dL, and creatinine 5.62 mg/dL. An antibiotic agent was given for pneumonia, steroid infusion for skin symptoms, intravenous infusion of monoammonium glycyrrhizinate for hepatic dysfunction and allergic reaction. Nineteen days after vaccination, pyrexia temporarily resolved, but pyrexia of 37.0°C or more recurred subsequently. Skin symptom remained unchanged. Twenty days after vaccination, during dialysis, decreased blood pressure occurred, and after dialysis, shock symptom was noted. A central venous line was established, and a cardiac stimulant, an antibiotic, steroid, and monoammonium glycyrrhizinate were administered. Blood pressure was stabilized from early evening to late evening. Before dawn, bradycardia, worsening of respiratory symptoms, and decreased blood pressure occurred. Despite supportive life-sustaining treatment, the patient eventually died. Remarks: The patient received an influenza A (H1N1) vaccination.	
8	Female in her 40s Adverse reactions: myocarditis The patient received a seasonal influenza vaccination. On the day of vaccination, in the evening, nausea, cough and pyrexia occurred and she visited a nearby hospital. Three days after onset of the symptoms, increased hepatic enzyme was noted. Five days after onset of the symptoms, blood pressure decreased and she was admitted to the hospital. Treatment with intraaortic balloon pumping and percutaneous cardiopulmonary support was started, but multi-organ failure progressed, and she was thus transferred to another hospital. At the time, she was put on bilateral ventricular assist device. Myocardial biopsy was performed simultaneously. Histological findings included multiple sites of inflammatory cell infiltrate consisting of eosinophils, neutrophils, and plasmacytes, and cardiomyocyte dropout. Acidophil granules were scattered. Fungus body was suspected, but based on a positive result on Kossa staining, it was concluded that calcium deposits occurred associated with cardiomyocyte destruction. While the patient was diagnosed with eosinophilic myocarditis, there was no increase in peripheral blood eosinophils. One hundred twenty days after onset of the symptoms, the patient died. Hepatic failure prevented her from receiving aggressive treatment. Remarks: This is a literature report (The 31st Cardiac Biopsy Conference, November 27 and 28, 2009)	In this case the patient experienced nausea, cough and pyrexia on the day of vaccination, and was admitted to hospital for increased hepatic enzyme and decreased blood pressure, and then diagnosed with myocarditis. She had no underlying disease. Although the series of the symptoms occurred after vaccination, causality to the influenza vaccination could not be evaluated due to insufficient detailed information.

Table 4 Summary of Sequelae Cases

No.	Case Summary	Review results of the Review Committee
1	Female in her 40s Adverse reactions: Guillain-Barre syndrome The patient received a seasonal influenza vaccination. Subsequently, Guillain-Barre syndrome developed, and she was transferred to another medical institution. Remarks: This was a case of vaccination in 2006.	In this case the patient was diagnosed with Guillain-Barre syndrome after vaccination. Causality to the influenza vaccination could not be evaluated due to lack of details
2	Female in her 50s Adverse reactions: Guillain-Barre syndrome The patient received a seasonal influenza vaccination. Two days after vaccination, weakness of both hands occurred. (Thereafter, she visited another hospital for physical deconditioning, but it is unknown whether she was diagnosed with Guillain-Barre syndrome at that time.) Twelve days after vaccination, she visited another medical institution. Nerve conduction tests showed neuropathy of bilateral upper- and lower-limb axonopathy type, and spinal fluid examination showed albuminocytologic dissociation. The patient was diagnosed with Guillain-Barre syndrome. Thirteen to 17 days after vaccination, she was admitted to the hospital and received high-dose globulin therapy. Twenty-one days after vaccination, she was discharged from the hospital in remission with mild wrist-drop of both upper limbs. Twenty-three days after vaccination, she was confirmed negative for anti-GM1 antibody and anti-GQ1b antibody. Thirty-three days after vaccination, muscular weakness of both upper limbs persisted.	In this case, the patient experienced the symptoms 2 days after vaccination and was diagnosed with Guillain-Barre syndrome 12 days after vaccination. Causality to the influenza vaccination could not be evaluated due to lack of details.
3	Female in her 70s Adverse reactions: sudden deafness suspected The patient received a seasonal influenza vaccination. Subsequently, Guillain-Barre syndrome developed and she was transferred to another medical institution. Remarks: This was a case of vaccination in 2006.	In this case the patient developed cough, nasal discharge, and malaise as well as deafness 3 days after vaccination and suffered persisting deafness. Causality to the influenza vaccination could not be evaluated due to lack of details.

Table 5 Adverse Reactions associated with Seasonal Influenza Vaccines in FY 2009 (reported regardless of causality)

	Total	Recovery	Death	Serious	Hospitalization	Sequelae	Other	N/A
Total	52	20	3	1	4	1	16	7
1 Immediate systemic reaction	8	5						3
1A Anaphylaxis (reposted)								
1B Systemic urticaria (reposted)	8	5						3
2 Encephalitis, encephalopathy								
3 Convulsion								
4 Movement disorder								
5 Other neurological disorders	3	1			2			
6 Local abnormal swelling (over the elbow)	3	1					1	1
7 Generalized rash	5	2					3	
8 Pyrexia of 39°C and more	5	1					4	
9 Other abnormal reactions	9	4		1			4	
10 Nonstandard reports	19	6	3		2	1	4	3
10A Local reaction (redness, swelling, etc.) (reposted)	6	3					2	1
10B Systemic reaction (pyrexia etc.) (reposted)	1							1
10C Other (reposted)	12	3	3		2	1	2	1

(Note)

1. Listed figures are provisional and subject to future change.
2. The Vaccine Adverse Reaction Reporting System is intended, based on Immunization Practices, to collect and provide the public with information on changes in the health of individuals who have been vaccinated as required by the Preventive Vaccination Law. This reporting system is limited to those individuals who receive routine vaccinations.